LETTERS TO THE EDITOR

Blockade of cholecystokinin-A receptors has no effect on dyskinesias in Parkinson's disease

Cholecystokinin is one of the most abundant neuropeptides in the human CNS. It coexists with dopamine in ventral tegmental and substantia nigra neurons in rodents and primates, but the coexistence is less obvious in normal humans.[1] It modulates central motor effects of dopamine through nigral or striatal cholecystokinin-A (excitatory) and cholecystokinin-B (inhibitory) receptors. The effect of the neuropeptide differs, however, depending on the animal species, the dose used, cotreatments, and site of injection.

Cholecystokinin is selectively decreased in the substantia nigra of patients with Parkinson's disease, and cholecystokinin-A antagonist binding is reduced in hemiparkinsonian monkeys. Cholecystokinin inhibits levodopa induced dyskinesias in parkinsonian monkeys,[1] but proglumide, a cholecystokinin antagonist, did not improve motor signs in dyskinesia free patients with Parkinson's disease.[2] Proglumide is, however, a weak non-selective cholecystokinin antagonist. Oral SR 27897B (SR; Sanofi Recherche), a highly selective and potent cholecystokinin-A receptor antagonist, penetrates the CNS and blocks cholecystokinin potentiation of dopaminergic neurotransmission.[3] We evaluated the potential antidyskinetic effects of oral SR in parkinsonian patients using a placebo controlled double blind study design and a single challenge of apomorphine, a test used to determine the antidyskinetic properties of associated treatments.[4] As cholecystokinin-A antagonism may modify gastrointestinal motility,[3] and consequently the kinetics of oral levodopa absorption, parenteral apomorphine was preferred to oral levodopa.

Nineteen patients with Parkinson's disease, who had motor fluctuations and levodopa induced dyskinesias for 6 months, were included in the study, which was approved by the local ethics committee. All patients gave written informed consent. Eighteen patients completed the study. Although patients in the placebo group tended to have a longer Parkinson's disease course, no significant difference was found between the two treatment groups for age, sex, or medical history (table 1).

Patients were randomly allocated to the SR group or a placebo group using a ratio of 2:1, and SR or placebo was given once a day for 14 days. The initial SR dose of 1 mg/day was increased to 2 mg/day after 7 days, if tolerated by the patient. The minimal dose of apomorphine inducing dyskinesias was determined for each patient before starting the study. Apomorphine was administered in the morning in a fasting condition, after a 3 day administration of domperidone (60 mg), and a 12 hour withdrawal of antiparkinsonian drugs. Motor disability (table 1) and dyskinesias were then assessed in each patient in two identical apomorphine tests, before (day 1) and after the 14 day treatment (day 14). During the 14 days, patients kept a diary of abnormal events with special attention to dyskinesias.

Table 1 Characteristics of the patients and clinical effect of the cholecystokinin antagonist SR27897, on parkinsonian motor disability and apomorphine induced dyskinesias

	Placebo group (n=6)		*SR 27897B group (n=12)*	
Characteristics of the patients (mean (SD)):				
Age (y)	56 (8)		56 (10.5)	
Sex (M/F)	4/2		4/9	
Disease duration (y)	17.3 (6)		12.5 (6)	
Duration of levodopa therapy (y)	16 (6)		10.1 (6)	
Daily levodopa dose (mg)	883 (370)		887 (415)	
Hoehn and Yahr score (on/off)	2.3 (0.5)/3.8 (0.8)		2.2 (0.8)/3.7 (0.9)	
Effect on motor disability (mean (SEM))	Day 1	Day 14	Day 1	Day 14
UPDRS III off state	52.5 (7.3)	57 (8.1)	47.6 (4.8)	45 (4.6)
on state	19.8 (3.6)	17.3 (2.9)	14.1 (2.3)	13.1 (2.4)
Motor improvement (%)†	61.8 (4.5)	67.1 (6.2)	68.4 (4.3)	72.6 (3.0)
Delay of dopaminergic action (min)	13.2 (3.4)	10.0 (1.4)	10.1 (1.2)	12.8 (2.5)
Duration of the on phase (min)	46.7 (5.8)	55.7 (6.9)	65.9 (4.9)	60.3 (6.4)
Effect on dyskinesia (mean (SEM)):				
Severity of the dyskinesia (score/min)*	3.5 (0.8)	3.9 (1.1)	3.6 (0.6)	3.1 (0.6)

UPDRS-III=unified Parkinson's disease rating scale, part III.
†Difference between UPDRS off and on, divided by UPDRS off.
*Student's *t* test: no significant difference between day 1 and day 14.

The primary end point was the severity of dyskinesias/minute as evaluated by a videotaped standard procedure.[4] The predominant type of dyskinesia (dystonic, ballistic, or choreic) and its severity from 0 (no abnormal movements) to 4 (abnormal movements resulting in severe disability) were scored once a minute for 90 minutes in the four limbs, trunk, neck, and face by one scorer (maximum score=28). Dyskinesia time profiles in each patient were also analyzed qualitatively by all investigators blind to treatment. The investigator and the patients globally assessed (from 0 to 5) changes in dyskinesia noted during the study.

Treatment with SR was tolerated well without marked adverse effects. One patient discontinued the study after 5 days of treatment due to severe dyskinesias and repeated falls. These problems were present before the study. Three patients (SR group two; placebo group one) stayed at the 1 mg dose level. Although three patients on SR and none on placebo reported an occasional increase in dyskinesias, daily levodopa induced dyskinesias were considered globally by both patients and investigators not to have been modified. The mean doses of apomorphine used for video testing were 5.0 mg (placebo group) and 4.6 mg (SR group). There was no significant difference in delay before turning on, the duration of the on state, the percentage of motor improvement, or in apomorphine induced dyskinesias between the two groups (table 1). Qualitative analysis failed to detect any differences either in the type of dyskinesias, their topography, or their timing (onset and end of dose dyskinesias, peak dose dyskinesias) before and after SR treatment.

In this study, no significant changes in drug induced dyskinesias and in motor disability were found when patients with Parkinson's disease were treated with the cholecystokinin-A antagonist SR 27897B. The fact that this selective antagonist was ineffective in our study may have been for several reasons. The dose may have been below or even above the response threshold. Indeed, in rats, striatal perfusion with high concentrations of cholecystokinin induces hypolocomotion, whereas perfusion with low concentrations induces dopaminergic-like contralateral rotation. The apomorphine test model may not be sensitive enough. This seems unlikely, however, as it has been used to show the antidyskinetic properties of fluoxetine, clozapine, and propranolol in small groups of patients.[4] Furthermore, it permits the study of a wide range of dyskinesias, from dystonia to ballic and choreic dyskinesia, which result from differential activation of dopamine receptors. Thus the absence of an effect of SR on any type of dyskinesia suggests that cholecystokinin may not modulate dopamine release at the level of striatal cholecystokinin-A receptors. However, as cholecystokinin-A antagonist binding has been found reduced in a model of hemiparkinsonism in the monkey, it cannot be totally excluded that the absence of effect of SR results from a reduction in the density of striatum cholecystokinin-A receptors in patients with Parkinson's disease. Moreover, the dopamine agonist apomorphine acts postsynaptically, whereas cholecystokinin might act presynaptically—for example, by modulating dopamine release. An effect of SR on dopamine release would not be detectable in the apomorphine test. Finally, cholecystokinin-A antagonist may not have been effective if the modulatory effects of cholecystokinin on dopamine tone is mediated only through cholecystokinin-B receptors.[5] A study of cholecystokinin-B antagonists and agonists should be considered in patients with Parkinson's disease.

In conclusion, this is the first administration in patients of a selective cholecystokinin-A antagonist. Our results show that, at least under our experimental conditions, defective dopamine systems in parkinsonian patients are not modified by the inhibition of cholecystokinin-A receptors.

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I ARNULF
M VIDAILHET
A-M BONNET
S DESCOMBES
C JAILLON
Y AGID
Clinical Investigation Center, Department of Neurology, UPRES EA 2397, and INSERM U289, Pitié-Salpêtrière Hospital, 47–83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France

C BREFEL
O RASCOL
Clinical Investigation Center, Department of Clinical Pharmacology and INSERM U455, Purpan Hospital, Toulouse, France

J XIE
P POLLAK
Neurological Clinic, Department of Neurosciences and INSERM U318, Michallon Hospital, Grenoble, France

F CATTELIN
Sanofi-Recherche, Gentilly, France

Correspondence to: Dr I Arnulf
isabelle.arnulf@psl.ap-hop-paris.fr

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Charles Bonnet's syndrome: complete remission of complex visual hallucinations treated by gabapentin

Apart from damage or dysfunction of the CNS visual hallucinations may also arise from a pure peripheral pathology caused by lesions of the optical nerves or an ocular pathology as in macular degeneration, retinopathy, or cataract. This association of impairment of peripheral vision and complex visual hallucinations in aged psychologically normal people is called Charles Bonnet's syndrome. Typically there are no concomitant psychotic symptoms and the patient is usually aware of the unreality of his experiences. However, despite a widespread agreement about hallmarks of the phenomenology, a universally accepted definition has not been found yet.[1]

Little is known about the underlying pathophysiology. A widely accepted hypothesis postulates a reduced afferent input causing a "release" with disinhibition of engrams in the visual association cortex that are experienced as hallucinations. Indeed a recent fMRI study has shown an increased activation of the ventral extrastriate cortex in Charles Bonnet's syndrome.[2] Some authors suggest that hallucinations in the syndrome may share a common mechanism that also evokes hallucinations in some central disorders (for example, after infarction of the visual cortex) involving cholinergic and serotonergic pathways.[3]

Although often neglected or misdiagnosed in clinical practice[4] a peripheral visual pathology seems to be an important differential diagnosis of complex visual hallucinations. In a large study of 500 visually handicapped patients Teunisse *et al*[5] found a prevalence of Charles Bonnet's syndrome of 11%. The occurrence of the syndrome was significantly associated with older age (>64) and a severe impairment of visual acuity (<0.3 in the best eye).

Therapeutic options for Charles Bonnet's syndrome still remain poor and of uncertain benefit for the individual patient. Even without any intervention in some patients the hallucinations can fade away within a few weeks or months. However, there are also many reports of a continuous course with ongoing tenacious hallucinations for up to 8 years.[6] An improvement of visual acuity—for example, after cataract extraction—or also a deterioration can eliminate the hallucinations.[7] Many of the widely used psychotropic drugs such as benzodiazepines, antidepressant drugs, or classic neuroleptic drugs have not been effective. Only a few reports exist of successful pharmacotherapy, with carbamazepin, valproate, melperone, or cisaprid.[8–11] Also, non-pharmacological strategies based on reassurance and self education can be helpful.[1] For instance, some patients reported an influence of intensive thoughts. Even admission to hospital interrupted the hallucinations in some cases; however they recurred after discharge.

We describe a patient with a 2 year history of Charles Bonnet's syndrome with macular degeneration, with persistent and frequent hallucinations that have disappeared after treatment with gabapentin.

The 86 year old woman had a 2 year history of complex visual hallucinations on being admitted to our hospital. A senile macular degeneration had been diagnosed by her ophthalmologist 10 years previously. She complained of a daily and repetitive occurrence of images predominantly showing human beings such as medieval women and knights in bright colours, but also torsos or isolated heads. None of the faces were familiar to her. They were of realistic size, coincided with normal perception of the external space, and mainly emerged when looking at a wall or lying supine facing the ceiling. The hallucinations were exclusively of a visual nature and static, but moved when she moved her eyes. They never occurred when her eyes were closed. She also sometimes experienced hallucinations of tiny homunculi strolling on the floor and climbing on her legs when she tried to step on them. Rarely, the content of the hallucinations changed while being watched—for example, from a female to a male head. The duration of the phenomena ranged from seconds to a few minutes. The patient recognised an increase in hallucinations during exhaustion or inflammatory diseases with raised temperature. A condition which regularly evoked hallucinations was using a mobile phone. A complex pattern of rhomboid shapes emerged with a short latency and faded away soon after having switched off the phone. The patient had full insight into the non-realistic nature of her experiences and she did not feel distressed by them. None the less, she argued that the hallucinations sometimes interfered with perception when she was driving a car; therefore convincing her to seek therapy.

We asked the patient to document the time and content of the hallucinations throughout the day in a pretreatment diary. It showed that they were most likely to occur in the morning and in the evening. The most prevalent features were parts of human beings, predominantly heads. Sometimes, objects such as old fashioned clocks or tombstones were described.

There was no psychiatric history. Medical history showed no diseases apart from hypertension and a severe polyarthrosis. She only irregularly took an antihypertensive medication (an angiotensin II antagonist and a diuretic) and pain killers (tilidine). Her general practitioner also prescribed Ginkgo biloba extract and pentoxifylline to treat the hallucinations, but without any effect. On admission to our hospital she was only taking homeopathic medication.

Neurological examination was normal. A dry atrophic macular degeneration was confirmed by our ophthalmologist. Visual acuity was 0.4 in the left eye and 0.6 in the right eye, without perimetric signs of scotomas. No cognitive dysfunction (mini mental state examination 29/30, above average performance in testing alertness, and selective attention) or additional psychotic symptoms could be found. Laboratory tests were normal. Her EEG and brain SPECT disclosed no pathology. Cranial MRI only showed an age related circumscribed frontal atrophy but no abnormalities in the brain.

We started pharmacotherapy with gabapentin (300 mg/day). The patient reported only one hallucinatory event on each of the next 2 days. After that, the hallucinations disappeared; confirmed in a follow up examination 3 months later. The medication has been well tolerated without any side effects. There was no visual deterioration, confirmed by an examination by her own ophthalmologist at this time.

In our case report the complex visual hallucinations, both normal sized and "Liliputian", accompanied by full insight as well as preserved cognitive skills without a specific brain pathology in morphological and physiological studies, fit in well with the typical clinical picture of Charles Bonnet's syndrome. Also the increase during the morning and evening has been described reminiscent of the emergence of hypnagogic hallucinations in normal subjects. It is noteworthy that visual acuity was less impaired than usually reported in patients with Charles Bonnet's syndrome, which emphasises that a severe loss of vision is not a necessary condition.

As already mentioned, the natural course of the hallucinations differs greatly between patients with Charles Bonnet's syndrome. It sometimes only covers a short period, with a spontaneous remission. Therefore, a therapeutic approach seems not to be necessary for all patients. None the less, an effective pharmacotherapy is needed for those with highly frequent and chronically ongoing hallucinations that are not responsive to non-pharmacological interventions and cause a considerable impairment of daily life. This reflects the situation in the patient presented, who came to our hospital to get an efficient therapy as she had a 2 year history of chronic hallucinations which had not responded to previous interventions. Facing the paucity of data in the field of therapeutic options we eventually considered gabapentin to be a likely favourable drug for treatment of Charles Bonnet's syndrome for the following reasons:

(1) Anticonvulsant drugs in general may influence abnormal neuronal excitations caused by release mechanisms. This is supported by two reports of an effective treatment of Charles Bonnet's syndrome with carbamazepin and valproate.[9 10]

(2) There is a wide non-epileptic use of gabapentin as well as of conventional anticonvulsant drugs including therapy of peripherally caused "phantom pains", possibly having similar pathophysiology in another modality.

(3) Compared with the above mentioned drugs gabapentin seems to have fewer side effects (for example, compared with carbamazepin or neuroleptic drugs, which often cause marked sedation or cognitive impairments) and fewer interactions with comedication, providing a safer application, especially in the predominantly elderly Charles Bonnet's syndrome population. The properties of gabapentin require less time for increasing the dosage as in many other antiepileptic drugs and therefore can possibly shorten the period of stay in hospital. However, there are conjectures that GABA related anticonvulsant drugs may cause visual field defects, which might be of interest especially in the already visually impaired patients with Charles Bonnet's syndrome. The exact action of gabapentin on neuronal systems has not been worked out but probably involves multiple mechanisms, apart from GABA.[12] By

contrast with many reports on vigabatrin, there has not to our knowledge been substantial evidence for a causal association between visual field defects and gabapentin, although transient tritanopia and critical flicker fusion paradigms might be slightly influenced by the drug.[13 14] Also in the patient reported here an ophthalmological follow up examination did not show a visual deterioration. None the less, further studies on treatment with gabapentin should consider this topic with special concern.

In our patient, a well tolerated low dosage application of gabapentin coincided with a full remission of the hallucinations within 2 days after having started the medication and no relapses were reported in a follow up examination 3 months later. Considering the 2 year history of continuous daily repeated hallucinations this strongly points to a causal correlation, suggesting gabapentin to be an efficient and safe treatment for Charles Bonnet's syndrome. This remains to be proved in a larger group of patients.

In view of the current data on Charles Bonnet's syndrome, therapeutic approaches should be adjusted for each patient as there are possibly interindividual inconsistencies in responsiveness to treatment.[15] To that end, a broader range of potentially effective drugs would increase the options.

M PAULIG
H MENTRUP
Neurologisches Krankenhaus München, Tristanstrasse 20, D-80804 Munich, Germany

Correspondence to: Dr M Paulig

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Paraneoplastic opsoclonus-myoclonus associated with renal cell carcinoma and responsive to tumour ablation

Opsoclonus is a rare but distinctive disorder of ocular motility, characterised by irregular, continual, and conjugated chaotic saccades of the eyes. It is increased with eye closure and with fixation, and it persists during sleep. When accompanied by other symptoms of CNS involvement, such as head and appendicular myoclonus and truncal ataxia, it constitutes a striking clinical picture, known as opsoclonus-myoclonus syndrome. Opsoclonus is relatively frequent in children, but it is rare in adults. In adults, the most common aetiology is idiopathic, accounting for about 50% of cases; usually these patients are younger than 40 and have a good prognosis. The second most common cause is paraneoplastic, responsible for 20% of cases. All paraneoplastic cases reported in the literature occurred in patients over 40. The most common tumours, which give rise to 70% of described cases, are breast and lung cancers (small cell lung cancer and adenocarcinoma). Because of the nature of the underlying lesion, the great majority of these patients die in a few months.[1] Whereas successful treatment of the malignancy results in a significant improvement in most children, the responses obtained in adults are rare.[2] Up to now, only one patient with a kidney tumour—namely, a papillary tumour—and opsoclonus-myoclonus has been reported in the literature, and he did not benefit from removal of the tumour.[3] We report a case of opsoclonus-myoclonus syndrome in a young adult patient with a renal cell tumour (RCC), who did not respond to medical therapy, but who dramatically improved after removal of the tumour.

He was a previously healthy 37 year old man who abruptly developed severe vertigo and gait unsteadiness. Subsequently, he developed chaotic eye movements, so severe that he could not open his eyes without vomiting. He could not even move his head without severe worsening of vertigo, eye movements, and nausea. He could neither stand nor walk because of ataxia and he complained of nervousness and emotional lability. Neurological examination disclosed coarse eye movements identifiable as opsoclonus. These movements, of variable amplitude, were present in a horizontal and, less often, in a vertical plane, without pauses between saccades, and greatly increased when attempting visual fixation in any direction. They persisted with eye closure and during sleep. At this acute stage opsoclonus was uninterrupted. Head and appendicular myoclonic jerks were induced by any attempt at truncal movements.

Laboratory tests, including complete blood count, routine chemistry, erythrocyte sedimentation rate, urinalysis, thyroid function and immunorheumatological tests were normal. His CSF was normal except for proteins, which were mildly increased (0.97 g/l); isoelectric focusing did not detect oligoclonal bands. Serum and CSF serological tests were negative for bacteria and different viruses (HIV 1–2; HVZ, CMV, HSV1+2: VCA, EBNA; adenovirus; parvovirus 19*; Borrelia; Listeria*). Brain MRI with and without gadolinium was normal. His EEG was diffusely slow. Thoracic CT was normal whereas abdominal ultrasound showed a 3.5 cm solid lesion, confirmed by abdominal MRI as a finely unhomogeneous mass, enhancing after gadolinium injection. Typical anti-onconeural antigen antibodies (anti-Hu, anti-Ri, and anti-Yo) were absent. A search for atypical antibodies was also performed by immunohistochemistry on rat brain serial cryostatic sections fixed by perfusion with 4% paraformaldehyde. The study was focused on the pons (paramedian pontine reticular formation and inferior olivary nuclei) and cerebellum (Purkinje cells and dentate nucleus), which are theoretically involved and that seem to be pathologically involved in inflammatory and degenerative processes in this eye movement disorder[4]; however no significant staining was found.

At the beginning of the symptomatology, treatment with clonazepam, thiamine, piracetam, and valproate, was started in an attempt to reduce neurological symptoms, without any benefit. Immunomodulators—namely, intravenous immunoglobulin (IVIg) (0.4 g/kg/day for 5 days) and prednisolone (50 mg/day)—were introduced after the diagnosis of the renal lesion and after the interruption of all previous drugs, but symptoms did not significantly improve. Ablation of the renal tumour was performed about 3 weeks after the beginning of the symptomatology. The cancer was a well differentiated RCC with a papillary differentiation (T1G1Nx); therefore the prognosis was excellent. In fact, tumour recurrence or diffusion at this stage of disease is very low, with a 5 year disease free survival rate of 100%.[5] The patient's serum did not stain cryostatic sections of his unfixed tumour. Just after removal of the tumour a slow but progressive improvement in the neurological symptoms started, beginning with an amelioration of opsoclonus, vertigo, and nausea. Eye movements became less frequent with pauses between each saccade becoming longer and longer, to disappear completely after 3 months. Some days after the intervention the patient began to eat and to spend a large part of the day with his eyes open. This progress allowed him to start physiotherapy. Six months after surgery the patient was completely normal and attending to his usual tasks.

This is the first report of an association between opsoclonus-myoclonus and renal cell tumour. We suggest that the presence of a kidney tumour must be taken into consideration every time an opsoclonus-myoclonus syndrome is seen, even in a young adult. This is essential as the early detection of such a tumour permits the removal of the mass in a very early phase, giving rise to a cure. Moreover, in our patient the surgical treatment resulted in the disappearance of the neurological symptoms, which had neither responded to strong immunosuppressive nor to any symptomatic medical therapy.

M C VIGLIANI
L PALMUCCI
P POLO
R MUTANI
D SCHIFFER
Dipartimento di Neuroscienze, Università degli Studi di Torino, Via Cherasco 15, 10126 Torino, Italy

S DE LUCA
A DE ZAN
Department of Surgical Sciences, Section of Urology, University of Turin, Italy

Correspondence to: Dr M C Vigliani
vigliani@usa.net

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Azathioprine treatment in multiple sclerosis; pretreatment assessment of metaboliser status

Azathioprine is a cytotoxic immunosuppressant drug used widely in clinical neurology as an adjunct to steroid treatment for autoimmune and inflammatory conditions. As a result of the relatively high cost and modest benefit of the newly licensed immunomodulatory therapies in the treatment of multiple sclerosis there has been a resurgence of interest in the possible benefits of azathioprine. A meta-analysis in 1997 suggested that it was as effective as newer treatments in increasing the proportion of patients who remain free of relapse at 2 years.[1]

The mode of action of azathioprine at the immune cell level remains unclear. It is converted rapidly in vivo to 6-mercaptopurine, which is extensively metabolised along three competitive routes (table 1).[2] Methylation catalysed by thiopurine transferase (TPMT) leads to the production of 6-methyl mercaptopurine. Wide variations in TPMT activity exist between patients and are determined by a common genetic polymorphism; 89% of the population have high TPMT concentrations, 11% intermediate concentrations, and 1 in 300 low or absent TPMT concentrations. A second catabolic route is oxidation with xanthine oxidase, which exhibits little interindividual variation in activity. The third route, catalysed by hypoxanthine guanine phosphoribosyl transferase, results in the formation of active thiopurine metabolites including 6-thioguanine nucleotides (6-TGN) which are thought to be responsible for the cytotoxicity of azathioprine.

In 1980 Weinshilboum and Sladek[3] proposed that the inherited variation in TPMT activity might represent one factor in individual variations in sensitivity to thiopurine drugs. The importance of a low activity of TPMT with an associated increase in 6-TGN in red blood cells in patients with bone marrow failure treated with azathioprine was reported by Leonard *et al*[4] in 1989. Since 1963 61 fatalities suspected to be associated with azathioprine have been reported to the Committee on Safety of Medicines (personal communication); 25 of these were classed as haemopoietic disorders. The importance of an inherited deficiency in thiopurine methyltransferase is mentioned specifically in the data sheet for Imuran (Glaxo-Wellcome).

Full blood count is a poor method of detecting early bone marrow toxicity as by the time changes have occurred dangerously high concentrations of 6-TGN may have accumulated. An alternative which allows this complication to be anticipated is the measurement of TPMT activity in red blood cells. This is a relatively cheap test (~ £26), performed on an EDTA blood sample, and genotypic testing may soon be clinically available Late onset myelosuppression has a more gradual onset and can be detected by changes in blood counts.

The overview of azathioprine treatment in multiple sclerosis published as a meta-analysis in the *Lancet* in October 1991[5] showed that the probability of freedom from relapse during the first, second, and third year of treatment was significantly greater in the azathioprine group, but the change in the expanded disability status scale (EDSS) was not significantly different. The authors concluded that it was debatable whether the slight clinical benefits outweigh side effects and that it is still not possible to predict which patients are likely to benefit from treatment with azathioprine. Although studies included in the Cochrane database mention morbidity in terms of decreased haematological indices and three mortalities said to be unrelated to multiple sclerosis or azathioprine, TPMT concentrations were not measured in any of the trials included in the meta-analysis.

Individual variation in TPMT may explain the variable toxicity and treatment response with azathioprine in multiple sclerosis. In addition, knowledge of TPMT status in patients with multiple sclerosis could identify those unsuitable for azathioprine treatment and those in whom the dose could be increased to the top of the therapeutic range secure in the knowledge of a very low probability of toxicity. It has been suggested that studies using azathioprine may fail to detect a therapeutic effect due to underdosage—if TPMT is measured this can be avoided.

Anticipation of azathioprine related toxicity and the tailoring of dose to the metaboliser status of individual patients might have considerable implications in routine clinical practice.

F J THOMAS
T A T HUGHES
Department of Neurology, University Hospital of Wales, Cardiff, UK

A ANSTEY
Department of Dermatology, Royal Gwent Hospital, Cardiff Road, Newport NP 20 2UB, UK

Correspondence to: Dr FJ Thomas

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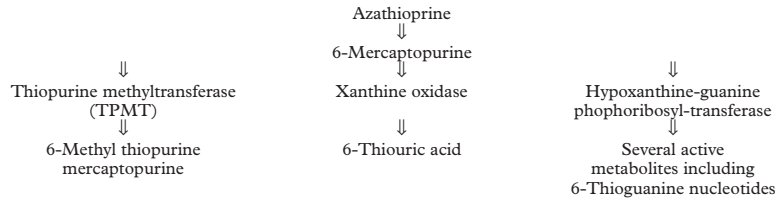
Table 1 Pathway of azathioprine metabolism



Migrainous brain stem disturbance in Norrie disease: case report

Norrie disease (or Norrie-Warburg syndrome) is a rare X linked disorder characterised by congenital blindness due to retinal hypoplasia. A third of patients may additionally have deafness and/or mental subnormality.[1] The gene has been mapped to Xp11.4-p11.3, in close proximity to the monoamine oxidase A and B (MAO-A and MAO-B) loci.[2]

We report a possibly unique case of Norrie disease in a man who described paroxysmal attacks of deafness, slurred speech, and somnolence from his late teens. The character of the attacks, in addition to their marked response to β blockade, argue for the enlargement of the phenotypic character of the disease to include migrainous aura affecting the brain stem.

A 38 year old left handed male computer consultant with Norrie disease sought neurological attention because of episodes of being unwell. He was born with no vision and atrophic eyeballs (phthisis bulbi). At the age of 18 he developed hearing loss necessitating hearing aids; after a period of worsening his hearing stabilised. His paroxysmal attacks began at this age, initially at a frequency of once every 4 or 5 months. During the year before neurological consultation, they increased to once every 2 or 3 weeks. They were predictably associated with stress or stress release. An attack typically began with a gradual deterioration (over a few minutes) of balance with further worsening in the hearing in his right ear, associated with a sense of fuzziness in his head. Occasionally he would experience a loud banging noise. The symptoms progressed to slurred speech, drowsiness, and almost complete deafness in the right ear. Observers described him as appearing pale and in discomfort during these episodes. The attacks could be truncated if he took a tablet or two of Praxilene (100 mg naftidrofuryl oxalate) sufficiently rapidly after the onset of symptoms. Otherwise, they would pass off after a few hours sleep. He did not describe a headache at any time; there was a dislike for food during the attacks but no nausea or vomiting.

His medical history otherwise consisted of mild asthma, controlled by occasional bronchodilator inhaler use. He had a nephew with Norrie disease. There was a family history of migraine in his mother.

General physical examination was normal. Neurological examination disclosed an articulate, insightful man with intact higher mental function. Both eyes were prosthetic. There was mild sensorineural hearing loss, worse on the right. The remainder of the neurological examination was unremarkable.

Brain MRI was normal. Further investigation of his monoamine oxidase status (see below) with urinary catecholamine metabolites, whole blood serotonin, and CSF

serotonin and dopamine metabolites was unfeasible for logistical reasons.

The time course, circumstances of precipitation, and positive family history suggested an acephalalgic migrainous disturbance. Despite his asthma, prophylaxis with β blockers was initiated (10 mg propranolol twice a day, building up to a long acting preparation (80 mg Inderal LA once daily). On review 6 months later, he reported a marked positive effect, having had only one, relatively mild attack during the period. His asthma remained well controlled on a more regular use of inhalers.

Norrie disease is a member of a family of disorders that result from mutations in genes occupying the proximal portion of the short arm of the X chromosome. The gene is flanked on either side by the MAO-A and MAO-B loci.[2] Point mutations in the Norrie gene lead to at least two other distinct clinical syndromes: familial and sporadic exudative retinopathy, and the retinopathy of prematurity.[1] More complex genetic defects arising from larger mutations including the Norrie locus have been described. Vossler *et al*[3] described three boys with Norrie disease and cataplexy with REM sleep disorganisation. All three patients had absent serum MAO-B activity; serum serotonin was increased, and plasma catecholamines were normal. Collins *et al*[4] reported on a male patient with a mutation spanning all three of the MAO and Norrie disease loci. The patient had severe mental handicap with myoclonus and stereotyped behaviour disorder; serum MAO activity was undetectable. Chen *et al*[2] drew attention to a family with pure MAO-A deficiency who had the phenotype of low normal intelligence, impulsivity, cardiovascular problems, and altered concentrations of amine metabolites.

To the best of our knowledge, there is no reported association between Norrie disease (and its genetic variants) and migraine. This is perhaps surprising considering what is the currently accepted wisdom on migraine pathophysiology.[5] This strongly implicates the serotonin-MAO axis—migraineurs have increased serotonin and diminished MAO platelet activity between attacks. Our patient was not investigated genetically or with serum MAO determination, but we surmise that he harbours at least a partial defect of MAO-A activity (the relevant enzyme for serotonin degradation). This presumably (and perhaps in conjunction with his familial tendency to migraine) is the metabolic basis for his symptoms.

We conclude that patients with Norrie disease who experience intermittent neurological dysfunction may benefit from β blockade.

We thank the patient for permitting us to report his case and Dr Tony Fryer for helpful discussion.

G P KALAMANGALAM
S J ELLIS
Department of Neurology, North Staffordshire Royal Infirmary, Stoke-on-Trent ST4 7LN, UK

Correspondence to: Dr S J Ellis

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Acute deterioration in Chiari type 1 malformation after chiropractic cervical manipulation

Type 1 Chiari malformation consists of caudal displacement of the cerebellar tonsils through the foramen magnum. It may also be associated with displacement of the medulla and hydromyelia or syringomyelia. The natural history is variable, with most patients presenting between the 3rd to 5th decades.[1] In a reported series of 71 patients, 69% presented with pain, 56% had weakness, 52% had numbness, and 40% complained of unsteadiness.[2] Mohr *et al*[1] classified patients' presentations into four main groups: syringomyelia, paraparesis, cerebellar, and "raised pressure'. We describe a patient with a previously relatively asymptomatic complex chiari 1malformation who acutely deteriorated after chiropractic manipulation of the cervical spine.

This white woman first presented at the age of 47 years in August 1995. She had sustained a mild "whiplash" injury in April 1995, having been struck at low speed from behind while sitting in a stationary car. She developed neck pain a few days later and this became progressively more annoying over the next 2 months. She then attended for chiropractic manipulation of the neck. This included repetitive high velocity, low amplitude thrusting movements at the base of the neck. Immediately after the therapy session, her neck pain worsened, spreading to involve the occiput, vertex, and frontal head regions. It was made worse with coughing, lifting, and bending over. She became aware of diplopia and intermittent difficulty swallowing. She had progressive gait instability when walking longer distances. In retrospect, she had many years of poor balance, with difficulty walking on uneven ground when wearing high heels. There was no sphincteric or sensory disturbance. Her history was unremarkable apart from total gastrectomy for a benign peptic ulcer. She was receiving regular B12 injections.

Examination showed normal visual acuity and funduscopic findings. There was bidirectional horizontal gaze evoked nystagmus and mildly impaired horizontal vestibulo-ocular reflex suppression. Vertical pursuit was abnormal with markedly impaired vertical vestibulo-ocular reflex suppression. There was right hypertropia on right gaze. There was no facial weakness or sensory loss. She had a "nasal" quality to her speech, with mild dysrhythmia with rapid consonants. The jaw jerk was pathologically brisk. There was increased tone in the lower limbs. Deep tendon reflexes were increased with positive Hoffman's sign and bilateral extensor plantar responses. She had a wide based gait with moderate truncal ataxia.

Plain radiographs of the neck disclosed assimilation of the posterior arch of C1 into the occiput, and abnormality of the dens. Brain MRI showed prolapse of the cerebellar tonsils through the foramen magnum to the level of the base of C2, with basilar invagination of the peg and angulation of the upper medulla (fig 1). There was mild midline cerebellar abnormality and distortion of the vertebrobasilar system. The aqueduct seemed normal. Laboratory tests disclosed compensated hypothyroidism.

She continued to deteriorate over the next 12 months, developing vertical nystagmus in the primary position, and became unable to walk unassisted.

In October 1996 she underwent a complex decompression procedure, with anterior removal of the anterior arch of C1, odontoid peg and clivus, and posterior removal of the occipital bone and attached occipitalised arch of C1. The surgery was complicated by development of pneumonia and a loculated empyema requiring a thoracotomy for decortication, and septic arthritis of a C1/C2 zygoapophyseal joint. She required a temporary percutaneous feeding gastrostomy.

Three years after surgery she has very mild residual cerebellar ataxia, eye movement disorder, and mild dysarthria. She is able to eat a normal diet and walks independently.

Various neurological complications have been described with head and neck manipulation. Case reports have most often documented vascular injuries and stroke syndromes.[3 4] Cervical manipulation has also been associated with spinal cord injuries and paraparesis,[5] phrenic nerve injury,[6] and various nerve root disruptions.

The patient reported here represents a case of occult complex Chiari 1 malformation, which acutely decompensated after neck manipulation. The mechanism of injury is probably related to vigorous head rotation with direct traction on the markedly angulated medulla. It is also possible that the anterior compression at the craniocervical junction was worsened by transient subluxation of an already abnormal atlantoaxial joint.

The frequency of complications after spinal manipulation is not known, although the usual public perception is that it is relatively risk free. This patient, and the literature would suggest that there is a real, if small, complication rate with a substantial long term morbidity and disability.

Certain conditions would seem to be absolute contraindications to chiropractic manipulation, and ideally these would be identified before proceeding. Plain radiographs of the spine, with emphasis on the occipitocervical junction, have been suggested as screening tools before manipulation.[3] If bony abnormalities or lytic changes are seen, then manipulation should be avoided. Certainly if this rule was followed, the patient would not have shown rapid deterioration. It should be emphasised however, that adult Chiari malformation is not uncommon and may not be associated with gross skeletal abnormalities.

Patients with previous symptoms of brain stem ischaemia should also avoid therapy. Others have also suggested that malignancy,

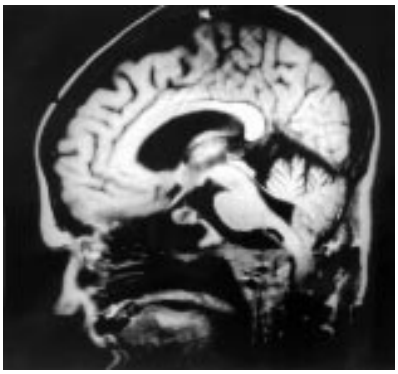

Figure 1 Preoperative T1 weighted sagittal MRI, showing cerebellar tonsillar invagination and angulation of the upper medulla, and abnormality of the dens and posterior arch of C1.

poorly controlled diabetes mellitus, anticoagulant therapy, infection, and hypermobility syndromes are absolute contraindications to spinal manipulation.[7] Despite these various precautions, many potentially vulnerable patients will be unidentified and it is likely that patients will continue to present with neurological complications after chiropractic manipulation.

We are grateful to Mr Alan Crockard, National Hospital for Neurological Disease, London, UK, for performing the surgery.

W K LEONG
A G KERMODE
Department of Neurology, Sir Charles Gairdner Hospital, Verdun St, Nedlands, Western Australia 6009

Correspondence to: Dr A G Kermode
akermode@ozemail.com.au

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CORRESPONDENCE

The EQ-5D—a generic quality of life measure—is a useful instrument to measure quality of life in patients with Parkinson's disease

We read with interest the recent article by Schrag *et al*,[1] in which the authors showed that the EuroQol-5D (EQ-5D) is a valid measure of quality of life in patients with Parkinson's disease. However, the authors neglected to mention two important aspects of the EQ-5D that differentiate it from typical quality of life instruments.

Firstly, the EQ-5D is a preference based measure. The summary score of the EQ-5D captures the strength of a person's preference for a given health outcome relative to other possible outcomes. These preferences (also called utilities) are measured on a scale from 0 to 1 where 0 represents death and 1 represents perfect health. The values derived from the EQ-5D can be used to compare health states in a quantitative way. For example, a health state with a value of 0.5 is half as desirable as perfect health. The scoring rule for the EQ-5D permits scores less than 0, implying that some health states may be worse than death.

Secondly, the index scores for the EQ-5D are intended to approximate general population preferences rather than the respondent's own health values. The EQ-5D values were developed based on ratings by a large, random sample of the adult population of the United Kingdom, The Netherlands, and Sweden.[2] As a result, the summary index score does not quantify the respondent's value of their own health, but rather the value that the general population would place on the respondent's health. By contrast, the visual analogue scores are direct measures of the value a respondent places on his or her own health. It is not surprising that the summary index scores and visual analogue scale scores are somewhat different in the study by Schrag *et al*.

These properties of the EQ-5D make it an indicated measure of health status for certain applications, particularly estimating health utility for cost-utility analysis. It is, perhaps, a fortunate accident that it is also a valid measure of quality of life in patients with Parkinson's disease.

A D SIDEROWF
Department of Neurology, University of Pennsylvania, 330 South 9th Street, Philadelphia, PA 19107, USA

R M WERNER
Department of Internal Medicine

Correspondence to: Dr A D Siderowf
adsiderowf@pahosp.com

1 Schrag A, Quinn N, Jahanshahi M, *et al*. The EQ-5D—a generic quality of life measure—is a useful instrument to measure quality of life in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2000;**69**:67–73.
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Selai et al reply:

We thank Siderowf and Werner for their interest in the EQ-5D and our work. They raise important points about the use and interpretation of generic quality of life instruments.

The valuation of health states raises many complex methodological and ethical issues and it is the topic of considerable debate in the literature.[1] Although we have participated in this debate,[2] we did not enter into a discussion of these issues in our recent paper because this was beyond the scope of that study.

The EQ-5D is a generic measure that has three distinct components, each providing separate data. The first part yields a simple descriptive profile of the respondents' own subjective health status in five dimensions. Secondly, the respondents next rate their own health on a visual analogue scale, calibrated 0–100. Thirdly, according to how the respondents have rated themselves on the descriptive profile, a utility value can be ascertained. Thus, the EQ-5D generates a cardinal index of health, giving it considerable potential for use in both economic evaluation and for ascertaining a person's subjective perspective of their own health status. The EQ-5D classification system defines a fixed number of health states, which may include health states valued worse than death, but leaves open the issue of what value should be assigned to each of those states.[3] Valuation data sets have been obtained in several countries, both European and non-European.

The evaluation of health related quality of life (HR-QOL) of patients with a given disease is generally measured using a disease specific instrument,—for example, the PDQ-39 in patients with Parkinson's disease. As these instruments are only applicable to patients with a particular disease, they do not allow comparisons across health conditions and are of limited use in economic studies. It is therefore recommended that a generic HR-QOL instrument be used in addition to disease specific measures. The generic measure must be tested and validated before use in the respective patient population. The purpose of our study was to test the validity and feasibility of two generic measures of HR-QOL (the EQ-5D and the SF-36) in patients with Parkinson's disease. The EQ-5D, a simple generic instrument, was shown to have good validity and feasibility and performed better than the SF-36 in this group of patients with Parkinson's disease.

C E SELAI*
A SCHRAG
N QUINN
M JAHANSHAHI
Institute of Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Correspondence to: Dr A Schrag

*Member of the EuroQol group

1 Drummond MF, O'Brien B, Stoddart GL, *et al*. *Methods for the economic evaluation of health care programmes*. 2nd ed. Oxford: Oxford Medical Publications, 1997.
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Cerebral malaria

Two items in the review of cerebral malaria by Newton *et al*[1] warrant comment. The first relates to corticosteroids in the treatment of cerebral malaria, and the second involves the definition of cerebral malaria.

The authors, citing Warrell *et al*[2] and Hoffman *et al*,[3] stated that steroids are contraindicated in cerebral malaria because they add risks without providing any benefit.

In late December 1965, I arrived in Vietnam as a neurologist with the United States Army Medical Corps., and for the next 6 months I was the only neurologist serving United States forces in Vietnam. I was attached to the 93rd Evaluation Hospital, which opened only 2 weeks before my arrival. As recounted in a recent article about my Vietnam experience,[4] two American soldiers with cerebral malaria died at the hospital during those 2 weeks, and the internal medicine specialists requested my involvement in all future cases. After reviewing the treatment protocols of the two soldiers, I decided that adding dexamethasone to the usual antimalarial regimen would be reasonable in patients with severe cerebral malaria. There was, I think, no literature at the time on the use of steroids; if there was, I certainly had no access to it in the combat zone.

During the next 10 months, we saw 19 patients with cerebral malaria, and they all recovered without any residual neurological dysfunction.[5] Our success with steroids prompted all the United States medical units in Vietnam to adopt the practice. A decade after the end of the Vietnam conflict, Warrell *et al*,[2] in a double blind trial, concluded that dexamethasone was both ineffectual and deleterious in cerebral malaria, and Hoffman *et al*[3] concurred. These two papers[2 3] are those usually cited by tropical medicine specialists (Newton and Warrell, 1998; White, 1999. See Daroff[4] for citations) in recommending

against the use of steroids in adult patients with cerebral malaria. Given the importance of the papers[2 3] buttressing the "no steroid" mandate, I will summarise them.

Warrell *et al*[2] studied Thai patients in a village hospital. There were two groups of 50 patients each; eight in the steroid treated group died, and nine of the untreated controls died. Hoffman *et al*[3] studied Indonesians in a provincial hospital with a mean age of 10.2 years, and found that four of 19 patients in both the treatment and control groups died. The two studies[2 3] had mortality rates of 17%–21%, and neurological residua in the survivors, which is in sharp contrast to the experience with United States troops in Vietnam. As mentioned, we had no deaths or residual neurological dysfunction in our 19 patients[5] and Dr Andrew Carr, the second neurologist in Vietnam, had an almost identical experience in 1966–7 using steroids in the sicker patients (personal communication). Blount (see Daroff[4] for citation) treated 24 patients with cerebral malaria with steroids and had no deaths. The three United States army hospital experiences in Vietnam in 1966–7 included a total of 62 patients with cerebral malaria liberally treated with steroids, with no deaths. There were no neurological residua in our series or Carr's[4]; Blount did not comment on residua. This compares with the 17% death rate in the study by Warrell *et al*[2], 21% in that of Hoffman *et al*,[3] and residual dysfunction in their survivors.

The cerebral malaria experience in the second world war is particularly relevant. Mortality rates in American troops were lower than in their Asian counterparts, and the rates in adults were lower than in children.[5]

Thus, I don't think that the conclusions of Warrell *et al*,[2] Hoffman *et al*,[3] and Newton *et al*[1] are applicable to western combat troops who are usually in excellent health before contracting malaria, and I continue to recommend steroids for an adult patient with cerebral malaria manifesting significant neurological dysfunction. I specify adults, as we lacked experience with children.

The definition of cerebral malaria is the other issue I have with Newton *et al*.[1] We diagnosed cerebral malaria when a patient with confirmed *Plasmodium falciparum* parasitaemia displayed signs of cerebral dysfunction that could not be explained by hyperpyrexia or detectable metabolic abnormalities.[5] The United States Army in the second world war also used this simple diagnostic criteria and experienced a similar occurrence rate. Our 19 patients with cerebral malaria were among about 1200 cases of falciparum malaria admitted during a 10 month period. This occurrence rate of about 1.6% is concordant with reports from United States hospitals in the second world war, which ranged from 1.2% to 2.3%.[5]

The neurological manifestations in our patients fell into five broad groupings.[5] Disturbance of consciousness was the most common (eight patients), and ranged from extreme lethargy to coma; on awakening, the patients displayed the expected transient cognitive disturbances before gradually returning to normalcy. Four patients had delirium, three movement disorders (tremor, myoclonus, chorea), one had a unilateral cerebral hemispheric syndrome, and three had acute personality changes (manifesting in two as a paranoid psychosis and in the other as a delusional state). In each of the these three, psychometric testing showed organic dysfunction that ultimately normalised (Blocker *et al* 1968; Kastl *et al* 1968. See Daroff[4] for citations). Previous studies, dating back to Anderson's 1927 monograph (see Daroff *et al*[5] for citation), reported similarly diverse manifestations in cerebral malaria.

Newton *et al*[1] commented about the loose definitions of cerebral malaria in the literature, often without evidence that confounding secondary causes of encephalopathy were excluded. We are confident that this criticism is not applicable in our series, nor others emanating from the medical experience among United States forces in Vietnam. Nevertheless, Newton *et al*[1] suggested a strict definition of cerebral malaria, requiring "a deep level of unconsciousness" or coma. Such restricted criteria might be justified in studies comparing treatment protocols, but to insist that a cerebral condition lacks degrees of severity is contrary to the experience of any neurologist. The all or none definition of cerebral malaria is simply not acceptable.

R B DAROFF
University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, Ohio 44106–5015, USA
rbd2@po.cwru.edu

1 Newton CRJC, Hien TT, White N. Cerebral malaria. *J Neurol Neurosurg Psychiatry* 2000; **69**:433–41.
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White and Newton reply:

Daroff has queried the World Health Organisation (WHO) definition of cerebral malaria that we quoted in our paper.[1] We pointed out that a patient with falciparum malaria with any impairment of consciousness or other sign of cerebral dysfunction should be treated as a medical emergency with parenteral antimalarial drugs. The point about the definition proposed by WHO,[2] is to allow a direct comparison between studies in which the clinical syndromes are precisely defined

This point is well illustrated by Dr Daroff's comments on studies of corticosteroids in malaria; he compares his studies on cerebral malaria, in which the cerebral involvement was described in terms of "extreme lethargy", "delirium", or "stupor"[3] to those in whom cerebral malaria was strictly defined.[4 5] It is difficult to compare the mortality in such disparate groups.

As for the continued use of corticosteroids in cerebral malaria, Daroff's recommendation is based on anecdotal experience during the second world war and Vietnam in the 1960s. There is little theoretical basis for using corticosteroids.[6] The two double blind, randomised control trials of dexamethasone failed to demonstrate any benefit from corticosteroids in adults with a precise definition of cerebral malaria.[4 5] Indeed the studies were associated with a significant increase in gastrointestinal bleeding,[4 5] infections,[4] and duration of unconsciousness.[4]

It is difficult to assess historical anecdotal evidence as there are many factors which may contribute, such as differences in the definitions of the clinical syndrome, drug resistance, and patient groups. Although the two randomised trials do not exclude a potential benefit, there is little substantial evidence to support the use. The onus is on the people who think that corticosteroids are beneficial, to provide more substantial data to support their conjecture, preferably as the results of a randomised trial.

C R J C NEWTON
Neurosciences Unit, The Wolfson Centre, Institute of Child Health, Mecklenburgh Square, London WC1N 2AP, UK

N WHITE
Centre for Tropical Disease, Cho Quan Hospital, Ho Chi Minh City, Vietnam

Correspondence to: Dr C R J C Newton
cnewton@kilifi.mimcom.net

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Treatment of paroxysmal sympathetic storm with labetalol

Do *et al* present a patient with paroxysmal sympathetic storm, and include a sample of the patient's ictal EEG recording.[1] It is stated that the absence of clear epileptiform activity serves as evidence against these episodes being epileptic in nature. However, if indeed the EEG recordings during an attack show significant slowing, as depicted in the EEG sample, this EEG change from a presumably normal EEG background rhythm at other times, would rather indicate that these events are, indeed, of seizure origin.

Deep seated epileptic foci very often do not project any sharply configured waveforms to the scalp surface; neither do they provide reliable localising information and can appear rather in a generalised fashion. In such cases, any reproducible and reliably observable EEG changes from the background rhythm that coincide with the clinical event are typically interpreted as evidence in favour of epileptic activity. Possible candidates for surgical treatment of their epilepsy would be further investigated with implanted electrodes in an effort to obtain EEG recordings from the closer vicinity of the presumed focus. This is obviously not a justifiable approach in this patient as surgical resection is not an option in this location.

Neither should successful treatment of specific symptoms during an attack with medication other that antiepileptic drugs necessarily be interpreted as evidence against the event being epileptic. In this case report, the patient's autonomic disturbances during the episode did respond to labetalol; however, this does not necessarily exclude a possibly epileptic origin as labetalol could only have obscured the clinically observable manifestations.

O BERNATH
Atkinson Morley's Hospital, Department of Neurology, Copse Hill, Wimbledon, London SW20 0NE, UK

1 Do D, Sheen VL, Bromfield E. Treatment of paroxysmal sympathetic storm with labetalol. *J Neurol Neurosurg Psychiatry* 2000;**69**:832–3.

Bromfield et al reply:

We appreciate Bernath's thoughtful comments concerning our case report of using labetolol to treat paroxysmal sympathetic storm. We agree that ictal EEG patterns can be quite variable and subtle, and that paroxysmal slowing can correspond to a seizure even without observable sharp waves or spikes. In this context, rhythmicity is generally viewed as a major characteristic of an ictal EEG, usually with a typical frequency evolution, sometimes accelerating after onset and usually slowing before stopping.[1] These characteristics were not seen in our patient. Furthermore, we should clarify that the background between these episodes was not normal, but rather showed a 6–8 Hz, somewhat disorganised posterior rhythm, with intermixed diffuse theta and some low voltage delta. We therefore interpreted the higher amplitude slowing during attacks, as seen in the previously published figure, as an arousal response. We have enclosed with this communication a sample from the same EEG study that shows the typical background activity followed by a definite arousal, corresponding to the notation of "noise"; this arousal is similar to that recorded during attacks (fig 1). In addition, we should have made it clear that, although later alert and responsive both during and between attacks, at the time this EEG was performed, before completing treatment of the shunt infection, he was moderately lethargic between attacks, and became more alert and agitated during them. Space limitations prevented our inclusion of this "baseline" EEG pattern during the initial report.

The fact that the patient responded to autonomic agents rather than to antiepileptic drugs is not a definitive argument against an epileptic origin, as noted by Bernath, although it provides at least circumstantial evidence. Furthermore, it seems unlikely that a diffuse EEG change, as shown in the original figure, would have only autonomic manifestations, and would be completely suppressed clinically by labetolol. Simple partial seizures with only autonomic manifestations would be more likely to show a unilateral temporal discharge or an unchanged EEG.[2]

For these reasons, we think that our patient in fact had paroxysmal sympathetic storm rather than multiple daily, prolonged autonomic seizures. As noted by Bernath, answering this question definitively would have required intracranial electrode placement, which was not clinically indicated in this case.

E B BROMFIELD
V SHEEN
D DO
Department of Neurology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA

Correspondence to: Dr E Bromfield
ebromfield@partners.org

1 Quesney F, Risinger MW, Shewmon DA. Extracranial EEG evaluation. In: Engel J Jr, ed. *Surgical treatment of the epilepsies.* 2nd ed. New York: Raven, 1993:173–95.
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Recurrent ptosis

In this *Journal*, Sieb and Hartmann described two patients with intermittent and alternating ptosis.[1] Intermittent sympathetic dysfunction causing a "partial" Horner's syndrome was suggested as the underlying pathogenic feature.

The photograph of the patient's eyelid shows a complete ptosis, which is not seen in

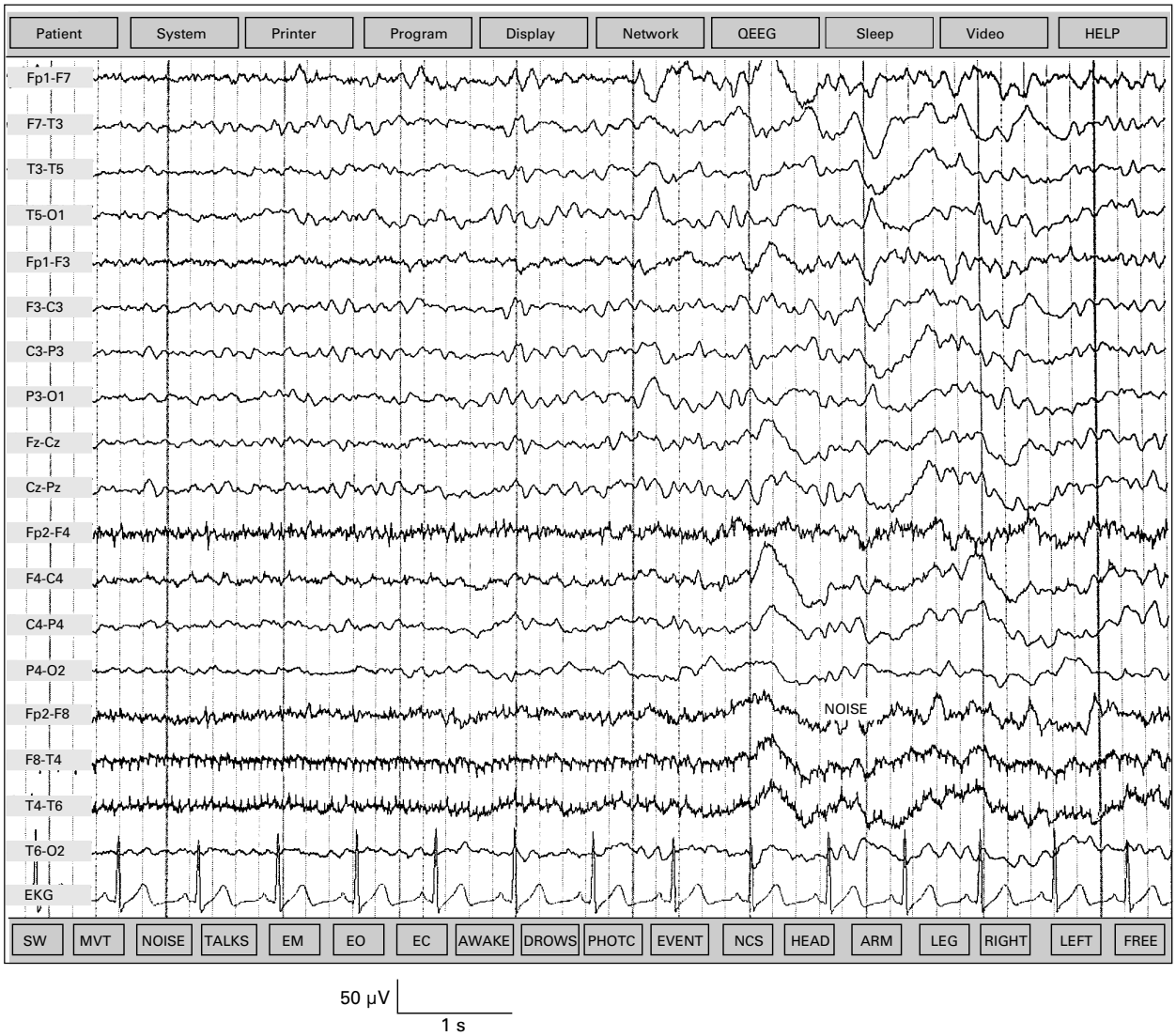

Figure 1 EEG, with longitudinal bipolar montage, recorded between attacks of paroxysmal sympathetic storm. There is a diffusely slow background, which increases in amplitude following an arousal, corresponding to the technician's notation of "noise".

Horner's syndrome because Müller's muscle contributes only to about 1.5 mm lid elevation.[2] More than sympathetic dysfunction alone is needed to cause the presented ptosis.

We recently reported a similar case in a 41 year old woman demonstrating involvement of both Müller's muscle and levator palpebrae superioris clinically and pharmacologically.[3] Orbital imaging showed enlargment of the levator palpebrae/rectus superior complex, which also suggests a local pathology. We proposed a local, possibly inflammatory process of the lid surface anatomy as described by Rice and Gray.[4] A similar explanation might account for the mild aching at the frontal region of the affected side in the patient of Sieb and Hartmann.

More recently a 62 year old man presented to our clinic with a 3 year history of recurrent right complete ptosis lasting 7 to 10 days, occurring once or twice a year with full recovery. The onset of the ptosis was associated with erythema and mild periorbital aching and swelling.

Unfortunately we have not yet been able to find an appropriate treatment. An initial trial with pyridostigmine using the rationale that 15%–20% of patients with myasthenia gravis have negative acetyl choline antibody[5] was disappointing,[3] as was treatment with nonsteroidal anti-inflammatory drugs and oral prednisolone.[1 3] Sieb and Hartmann tried the serotonin antagonist pizotifen and prednisolone also without significant improvement.

We do not know the reason for the recurrent complete ptosis in our two patients. Neither can we be sure that the siblings described by Sieb and Hartmann have the same disorder, particularly as in these patients the side of the ptosis alternated.[1] However, we suggest that the syndrome must be due to local disease causing loss of function of the levator palpebrae superioris muscle either alone or in addition to Müller's muscle.

A PETZOLD
G T PLANT
National Hospital for Neurology and Neurosurgery, Queen Square, London WC1 N3BG, UK

Correspondence to: Dr A Petzold
a.petzold@ion.ucl.ac.ak

1 Sieb JP, Hartmann A. Relapsing alternating ptosis in two siblings. *J Neurol Neurosurg Psychiatry* 2000;**69**:282.
2 Small RG, *et al.* The effect of phenylephrine on Müller's muscle. A blepharogram study of eyelid motion. *Ophthalmology* 1995;**102**:599–606.
3 Petzold A, Plant GT. Recurrent ptosis in an adult due to isolated paresis of the levator palpebrae superioris and Müller's muscle of unknown aetiology. *Neuro-Ophthalmology* 2000; **24**:279–82.
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5 Vincent A, Lily O, Palace J. Pathogenic autoantibodies to neuronal proteins in neurological disorders. *J Neuroimmunology* 1999;**100**:169–80.

Sieb and Hartmann reply:

We greatly appreciate the interesting comments of Petzold and Plant who described two sporadic patients showing clinical similarities to our siblings.

Unfortunately, we cannot provide additional evidence for their suggestion that local disease of the Müller's muscle and the levator palpebrae superioris might cause relapsing, alternating ptosis. Magnetic resonance studies of the orbita as proposed by Petzold and Plant did not show any pathology in one of our patients during an episode of ptosis.

The literature states commonly that oculosympathetic paresis results only in slight upper eyelid ptosis of 1 to 2 mm.[1] However, our clinical experience in patients with Horner's syndrome due to carotid artery dissection is different. We still think that an intermittent sympathetic dysfunction is the most likely explanation for the familial disorder observed by us. Hopefully, investigation of additional patients will shed light on the pathology of this unusual disorder.

J P SIEB
Max-Planck-Institute of Psychiatry, Kraepelinst 2–10, Munich, D-80804, Germany

A HARTMANN
University Hospital Department of Neurology, Sigmund-Freud Strasse 25, Bonn, D-53105, Germany

Correspondence to: Dr J P Sieb
sieb@mpipsykl.mpg.de

1 Patel AD. Autonomic nervous system and the eye. In: Vinken PJ, Bruyn GW, eds. *Handbook of clinical neurology: the autonomic nervous system, part I.* Amsterdem: Elsevier, 1999:399–435.

Management of intracranial bleeding associated with anticoagulation: balancing the risk of further bleeding against thromboembolism from prosthetic heart valves

We read with interest the article by Crawley *et al*.[1] We respectfully take issue with the authors.

(1) In this article on the management of intracranial bleeding associated with anticoagulation, the authors reported on a patient who had an "intracerebral haematoma" and later developed two new "intracranial haematomas" after heparin therapy. We hope that the authors were referring to either lobar haemorrhage or basal ganglia haemorrhage. If the patient had a subdural haematoma, also classified under intracranial haemorrhage, then a surgical procedure as well as discontinuation of anticoagulation and reversal would have been the preferred treatment.

(2) In their review of the literature, the authors did not discuss the articles by Wijdicks *et al* and Babikian *et al* on the relative safety of discontinuation of oral warfarin after intracranial haemorrhage in patients with mechanical heart valves.[2 3] These authors have found that temporary discontinuation of warfarin for 1 to 2 weeks was relatively safe.

(3) Crawley *et al* estimated a 0.016% daily risk of embolism or 0.67% over 6 weeks.[1] In our experience, although the risk is relatively low, it is in the order of 3% over 30 days.[4]

(4) Crawley *et al* correctly stated that having reversed anticoagulation in patients with prosthetic heart valves, it is uncertain when to restart it.[1] None of the patients in our experience had recurrence of intracranial haemorrhage on restarting warfarin (after a short period of discontinuation) during their stay in hospital.[4] Thus we do not recommend a prolonged period of warfarin discontinuation in patients who are at high risk of embolisation. Additionally we recommend that these patients be screened with echocardiography in evaluating the risk-benefit ratio of warfarin discontinuation and the urgency of restarting anticoagulation.

T G PHAN
E F M WIJDICKS
Department of Neurology, Mayo Clinic and Foundation, W8A, 200 First Street Southwest, Rochester MN 55905, USA

Correspondence to: Professor E F M Wijdicks
wijoe@mayo.edu

1 Crawley F, Bevan D, Wren D. Management of intracranial bleeding associated with anticoagulation: balancing the risk of further bleeding against thromboembolism from prosthetic heart valves. *J Neurol Neurosurg Psychiatry* 2000;**69**:396–8.
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3 Babikian VL, Kase CS, Pessin MS, *et al*. Resumption of anticoagulation after intracranial bleeding in patients with prosthetic heart valves. *Stroke* 1988;**19**:407–8.
4 Phan TG, Kott M, Wijdicks EFM. Safety of discontinuation and resumption of anticoagulation in patients with intracranial hemorrhage at high thromboembolic risk. *Arch Neurol* 2000;**57**:1710–13.

Wren replies:

We fully agree with Phan and Wijdicks that if a patient has a subdural haematoma while on treatment with warfarin surgical drainage might be required. The particular patient reported had recurrent lobar haemorrhage.[1] Photographs of the brain CT were supplied but not published.

We are aware of the articles by Wijdicks *et al*[2] and Babikian *et al*[3] as well as the recently published article by Phan *et al*,[4] which is an extension of the previous article published by Wijdicks *et al*.[1] The dilemma of reinstituting anticoagulation for patients with cardioembolic sources and intracranial haemorrhages is discussed by Hacke[5] in the editorial accompanying the recent paper by Phan *et al*.[4] Of particular interest is the apparent paradox between the reported embolic risk without anticoagulation with modern artificial heart valves in the range of 4 per 100 patient-years and observed risk in the order of 3% over 30 days in the retrospective studies of Phan *et al* going up to 20% in the study of Bertram *et al*.[4 6]

We agree with Phan and Wijdicks and Wijdicks *et al* that patients at high risk of embolisation should have a limited period of warfarin discontinuation and that each patient needs to be assessed individually as suggested by Hacke.[5] We also agree with Hacke's suggestion that a prospective registry would be very useful given the difficulties of setting up any form of randomised control trial. The potential prothrombolic effects of haemorrhage and reversal of anticoagulation are also subjects that merit investigation with, for example, thromboelastography.

D R WREN
Department of Neurology, Atkinson Morley's Hospital, Copse Hill, Wimbledon SW20 0NE, UK

1 Crawley F, Bevan D, Wren D. Management of intracranial bleeding associated with anticoagulation: balancing the risk of further bleeding against thromboembolism from prosthetic heart valves. *J Neurol Neurosurg Psychiatry* 2000;**69**:396–8.
2 Wijdicks EF, Schievink WI, Borwn RD, *et al*. The dilemma of discontinuation of anticoagulation therapy for patients with intracranial haemorrhage and mechanical heart valves. *Neurosurgery.* 1998;**42**:769–73.
3 Babikian VL, Kase CS, Pessin MS, *et al*. Resumption of anticoagulation after intracranial bleeding in patients with prosthetic heart valves. *Stroke* 1998;**19**:407–8.
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6 Bertram M, Bonsanto M, Hacke W, *et al*. Managing the therapeutic dilemma: patients with spontaneous intracerebral haemorrhage and urgent need for anticoagulation. *J Neurol* 2000; **247**:209–14.

Delirium episode as a sign of undetected dementia among community dwelling elderly subjects

Rahkonen *et al*[1] examine the complex issue of outcome after an episode of delirium and, in particular, whether an episode acts as an indicator of undetected dementia. Poor cognitive outcomes, including dementia, are well recognised after delirium but it is unclear whether delirium is merely a marker for dementia or if an episode contributes to the development of enduring cognitive impairment, possibly by a neurotoxic or kindling-type mechansm. Patients with mild cognitive impairment were not excluded at the outset but it is clear that there was a relation between mini mental state examination (MMSE) scores immediately after resolution of DSM IIIR delirium and risk of subsequent dementia. Given that persistent symptoms are common in delirium,[2] one possible explanation is that these cases reflect unresolved subclinical delirium or that incomplete treatment of delirium is a risk factor for subsequent cognitive decline.[3] The data should allow estimation of the frequency of dementia in those patients with MMSE scores within the normal range after full resolution of DSM IIIR delirium. This information is highly relevant to planning of post-delirium management and although the MMSE does not provide a sensitive measure of the neuropsychological disturbances of delirium, may shed some light on whether these findings relate to persistent cognitive deficits of delirium that are measured on the MMSE.

D MEAGHER
Department of Psychiatry, Midwestern Regional Hospital, Dooradoyle, Limerick, Eire

Correspondence to: Dr D Meagher
davidjmeagher@ireland.com

1 Rahkonen T, Luukainen-Markkula R, Paanila S, *et al*. Delirium episode as a sign of undetected dementia among community dwelling eldely subjects: a 2 year follow up study. *J Neurol Neurosurg Psychiatry* 2000;**69**:519–21.
2 Levkoff SE, Evans DA, Liptzin B, *et al*. Delirium: the occurrence and persistence of symptoms among elderly hospitalised patients. *Arch Intern Med* 1992;**152**:334–40.
3 Meagher DJ, Trzepacz PT. Delirium phenomenology illuminates pathophysiology, management and course. *J Geriatr Psychiatry Neurol* 1998;**11**:150–7.

Rahkonen and Sulkava reply:

We thank Meagher for his interest and for his comments on our paper. In the Kuopio delirium study, the disappearance of delirium (according to the DSM-III-R) was ascertained carefully. Instead of being discharged to their own homes (after the treatment of delirium and its underlying causes) the patients were transferred to a rehabilitation centre. During the 7 to 14 days stay in the rehabilitation ward the disappearance of delirium was confirmed. However, some symptoms also appearing in delirium, such as disturbances of the sleep-wake cycle or mild memory deficits, may have still been detected in these elderly patients, but they did not fulfil the diagnostic criteria for delirium any more.

In the Kuopio delirium study, 27% of the community dwelling elderly patients without serious predisposing factors for delirium were diagnosed as having mild dementia immediately after the resolution of the delirium. The rate of subsequent dementia in the remaining non-demented patients was three out of 11 (27%) with the initial score on the mini mental status examination 24 or over after the delirium subsided (the incidence rate of dementia was 18.2/100 person-years). In the patients with an MMSE score less than 24 the rate of subsequent dementia after resolution of delirium was 11 out of 26 patients (42%) (the incidence rate of dementia was 25.4/100 person-years). However, in our article we published only the rate of the subsequent dementia in all the patients. The number of patients in the groups based on the MMSE scores was small and the usefulness of the scores in diagnosing dementia was limited in these elderly patients (mean age 82 years). In our study, no corrections were made to the scores of the MMSE test because of vision or hearing impairment or limited education.

T RAHKONEN
R SULKAVA
Division of Geriatrics, Department of Public Health and General Practice, University of Kuopio, Finland

Correspondence to: Dr T Rahkonen

CORRECTIONS

Bhakta B, Cozens JA, Chamberlain MA, *et al*. The impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial. *J Neurol neurosurg Psychiatry* 2000;**69**:217-21.

In table 2, p219 in the column relating to carer burden, BT-A, the values −0.77 (−1.8, 0) should read −0.67(−1.8, 0) and −1.0 (−2.0, 0) should read −0.5(−2.0, 0)

Bradshaw JL, Mattingley JB. Allodynia: a sensory analogue of motor mirror neurons in a hyperaesthetic patient reporting instantaneous discomfort to another's perceived sudden minor injury?. *J Neurol Neurosurg Psychiatry* 2000;**70**:135-6. On page 136, para 3, line 8, the phrase "don't do that (meaning not to show him); he actually felt it" should have read "don't do that (meaning not to show him suddenly); he actually felt it".

Without the word *suddenly* the significance may be lost—It was because he "received the message suddenly" that he felt it (the experience of hyperaesthesia).

BOOK REVIEWS

Essentials of Clinical Epilepsy: 2nd Edition. By A GUBERMAN and J BRUNI. (Pp 207, £27.50). Oxford: Butterworth Heinemann, 1999. ISBN 0 7506 7109 2.

The authors of this text have sought to provide a handbook in which they present the core clinical knowledge on epilepsy while aiming to be comprehensive and up to date. Chapters cover the usual topics from epidemiology through to surgical treatment and this slim volume certainly packs in a huge amount of information. The reading lists are very useful with statistical information and data from up to date studies. Inevitably a book whose text is made up almost entirely of bullet points proves very difficult to read, and this format does not allow enough space for critical appraisal of the reference studies which the reader will hopefully be prompted to look up. The authors practical approach to managing epilepsy is useful and I would have liked to have seen more of this. Anticonvulsant drugs are listed with standard accounts of pharmacokinetic and pharmacodynamic data. Most readers would have been interested in a discussion of the relative merits of the newer anticonvulsant drugs and the quality of evidence supporting their use in comparison with the older drugs.

This is an excellent little handbook well suited as an introductory reference text for the authors stated target audience of residents in training and general physicians.

S J WROE

Central Nervous System Diseases: Innovative Animal Models From Lab to Clinic. Edited by D I P EMERICH, R L DEAN III, and P R SANBERG. (Pp 512, US$145.00). New Jersey: Humana Press, 2000. ISBN 0 896 03724 X.

This book takes as its main theme the neurodegenerative disorders and animal models of them for assessment and treatment. The book divides into five sections and concentrates on Alzheimer's, Parkinson's and Huntington's disease along with traumatic-ischaemic brain damage before concluding with some clinically relevant topics. The authors of each chapter are leaders in their field so that the accounts are generally well written, up to date, and authoritative—although some fields move so fast that some chapters in this book are already out of date. For example, the chapter on transgenic Huntington's disease mouse models by Gill Bates and coworkers is already missing some new interesting pieces of information on the possible pathogenesis of this condition. This having been said the large section, devoted to Huntington's disease in this book is welcome given just what an exciting field of research this is at the moment.

The overall structure of this book using sectional headings to group chapters is helpful, although the chapters themselves are a little uneven in their presentation. For example, the chapter on neural grafting by Roitberg *et al* consists of 27 pages of solid text with no figures whereas the chapter by Hantraye *et al* on primate models of Huntington's disease combines figures and text. The result is that the second is more accessible whereas the more wordy chapters are off putting even to those of us who are interested in the field. This also applies to the opening chapter on the cholinergic hypothesis of Alzheimer's disease, which can derail the reader before he has really got interested in the rest of the book.

This book presents an interesting collection of chapters, which provides a useful adjunct to those involved in research in this area of neuroscience, but It is not a book that will appeal to neurologists unless they are keen to update themselves on the emerging new therapies being developed in laboratories around the world. It is therefore a useful addition to the libraries of a few, rather than many which is a pity given its content and relevance to neurology in the next century.

ROGER BARKER

Treatment of Neurological Disorders with Intravenous Immunoglobulins. Edited by GERARD SAID (Pp 200, £24.95). Published by Martin Dunitz, London, 2000. ISBN 1 85317 758 X.

Over the past decade the introduction of high dose intravenous immunoglobulin (IvIg) therapy has transformed the treatment of some neuromuscular diseases, particularly multifocal motor neuropathy with conduction block, for which there is no satisfactory alternative therapy. The appearance of this small multiauthor handbook on the use of IvIg in the treatment of neurological disorders is timely. It has been well edited to produce a clear, easily readable, and relatively even style. The tables are useful and well produced. In general, the authors have stuck to the brief of balancing the relative merits of IvIg and conventional therapies for their chosen neurological disorder. However, one or two have used the book as the vehicle for a more general discussion on their chosen disease, accompanied by relatively brief comments on the particular part played by IvIg therapy.

All regular users of IvIg therapy must be intrigued by the unsolved mystery of its mode of action. The first chapter of this book considers its possible modulatory effects on a myriad of immunological pathways and mechanisms. Initially we all assumed that IvIg contains pooled naturally occurring anti-idiotypes which neutralise the patient's own pathogenic antibodies. Yet pathogenic antibodies have not been identified as the cause of most inflammatory neuropathies which respond to IvIg, and after all this time searching one wonders whether they ever will be. It is surprising that nobody has reported whether IvIg contains natural anti-idiotypes to the well characterised antiacetylcholine receptor antibodies which occur in myasthenia gravis, a disease for which IvIg seems to be effective according to recent trial evidence. This question of anti-idiotypic activity has been explored in the Lambert-Eaton myasthenic syndrome without disclosing obvious evidence of their existence against antibodies to the voltage gated calcium channel. As a frequent observer of the almost magical effect of IvIg in patients with multifocal motor neuropathy, I never fail to be struck by the clear benefit which regularly appears within 48 hours of the first infusion, with improved strength of muscles which may have been weak for years. Surely this rapidity of the effect of IvIg in reversing nerve conduction block is telling us something. It seems too quick to be accounted for by some notion of anti-idiotypic neutralisation of pathogenic antibodies, which would be expected to be firmly bound to the target tissue anyway. Possible explanations are raised in chapter 1, although they are not considered specifically in relation to this astonishingly prompt clinical effect. IvIg can modulate T cell control of the production of cytokines, including tumour necrosis factor-α, which may have the potential to cause nerve conduction block.

Inevitably much of this book addresses the principal role of IvIg in everyday neurological practice: the treatment of idiopathic demyelinating and conduction block polyneuropathies. In this book, motor neuropathy with conduction block and multifocal sensory demyelinating neuropathy are juxtaposed as rather distinct clinical entities; the second being christened the Lewis-Sumner syndrome. But given the high occurrence of rather non-specific and minor sensory symptoms in patients with multifocal motor neuropathy, and the documentation of sural (sensory) nerve abnormalities in such patients, can we consider these two syndromes as separate, or are they simply peaks within a mountain range? Later on this particular chapter considers whether diabetic proximal neuropathy might benefit from IvIg treatment, given recent evidence of inflammatory infiltrates in cutaneous branches of the femoral nerve, but no clear supporting evidence is presented for this therapeutic notion. The account of the role of IvIg in standard chronic inflammatory sensorimotor demyelinating polyneuropathy is usefully comprehensive. But despite factually correct and well balanced arguments concerning the relative merits of plasma exchange in IvIg in this condition, the book somehow fails to transmit a perspective of when particular clinical circumstances presented by CIDP may merit such therapies, and when to choose each of them. Should plasma exchange be used before IvIg given that it seems effective in about 80% of such patients compared with 65% for IvIg? And if plasma exchange is only partially effective, if it has been given first at least it won't have removed any IvIg administered as ancillary treatment. In Guillain-Barré syndrome the advice, quite rightly, is to give IvIg rather than plasma exchange in patients with potentially severe disease. Yet we remain ignorant of the long term benefit of either of these treatments in a disease which is regarded by many undergraduate textbooks as being relatively benign if you survive the bulbar and respiratory failure. Yet in reality Guillain-Barré syndrome leaves 16% unable to walk at a year, and up to 5% dead, despite IvIg or plasma exchange therapy. It would have been good to hear more on the Baltimore view of whether the long term outcome is better after IvIg than plasma exchange in the acute motor axonal subgroup of Guillain-Barré syndrome. This was an intriguing conclusion of subgroup analysis of the Dutch Guillain-Barré Study Group.

The other disease-specific chapters of the book address less well established, or minority indications for IvIg. These range from useful discussion on the surprisingly differential benefits of IvIg in the three forms of inflammatory myopathy, to a relatively small trial suggesting partial effectiveness in multiple sclerosis, and largely anecdotal evidence of benefit for the neurological complications of Behçet's syndrome and intractable childhood epilepsy syndromes. Some of these disorders can cause distressingly severe neurological disability. It will be useful to accumulate more data about the possible value of IvIg in treating them whilst acknowledging that it will be difficult to undertake large formal controlled clinical trials. And no doubt matters will be even more difficult in multiple sclerosis, where any future trials of IvIg may have to be in the form of add on therapy to other better established yet only partially effective treatments for the disease, such as β-interferon.

The final section of this book will be of great help to neurologists. It concerns the rather dry subject of preparation of IvIg, and its safety and tolerability. As any regular IvIg user knows, these questions crop up regularly. The clear and succinct guidance provided by this book is welcome. For instance, tabulation of the characteristics of the 18 commercially available IvIg products compares factors such as the sugars/stabilisers which are used in each; these may be related to some of the side effects. A review of the different methods for inactivating known infectious agents which may be present in the parent plasma pool reminds us that, whereas each method is highly effective, none of the current processes can guarantee total inactivation of infectious viral particles. There is practical advice about how to manage or offset the often encountered, medically trivial, yet none the less irritating, side effects which can occur during infusion. Many patients require regular IvIg for many years, and this volume could have provided more practical guidance on assessing whether it works in an individual patient, whether it works usefully in overcoming disability, and how patients and their families can be trained for domiciliary administration of IvIg.

A useful little book to keep in your office if you use IvIg regularly to treat neurological diseases. But it leaves untouched some of the most fascinating questions posed by IvIg. Why does it produce its effect so quickly? Why is it so effective in a supposed autoimmune disease, multifocal motor neuropathy, which is worsened by prednisolone therapy? Surely the answers will illuminate the pathogenesis of diseases such as multifocal motor neuropathy.

MICHAEL DONAGHY

Parkinson's Disease and Movement Disorders. Diagnosis and Treatment Guidelines for the Practicing Physician. Edited by CHARLES H ADKER and J ERIC AHLSKOG (Pp 480, US$ 125.00). Published by Humana Press, New Jersey, 2000. ISBN 0 896 03607 3.

The authors state that this book is aimed at the primary care physician or perhaps the "general" neurologist who is not an expert in the movement disorders field. As such, they have emphasised the clinical aspects of each condition including differential diagnosis with only an outline of the various treatment options.

It is divided into five sections. The first covers basic principles taking us back to the basic phenomenology of movement disorders and also basic neuroanatomy. There then follows an inappropriately complex chapter on motor speech disorders which is out of place in such a volume. Section two covers all aspects of idiopathic Parkinson's disease. As is common with multiauthor texts there is a great deal of repetition between the different chapters on the epidemiology, aetiology, pathophysiology, and clinical features of the condition. The chapters on neuroprotection and symptomatic therapy for the condition are more balanced and divided into sections specifically aimed at the less experienced clinician. However, they only cover North American practice where tolcapone remains available, whereas madopar, apomorphine and cabergoline are not. The chapters on associated problems such as sleep disorders, autonomic dysfunction, psychiatric problems, and surgery for Parkinson's disease are shorter and thus more suitable for the busy general practitioner. The third section covers Parkinson's plus syndromes including progressive supranuclear palsy and multiple system atrophy. These chapters are more balanced but then spinocerebellar degenerations suddenly appear and in considerable detail instead of being placed in a separate section on ataxic disorders. Whether chapters on corticobasal degeneration and primary degenerative dementia should be included in a book for general practitioners is a mute

point. Section four covers hyperkinetic movement disorders with separate paragraphs on tremor disorders, essential tremor, dystonia, hemifacial spasm, Huntington's disease, and tardive dyskinesias. The detailed explanations of myoclonus and the stiff person syndrome are inappropriate in such text. The final miscellaneous section comprises Wilson's disease, gait disturbance, and post-traumatic and psychogenic movement disorders. Much of this is also too specialised.

As a text for the general practitioner to either read or use as a reference source, this book is far too long. This stems from the repetition in the earlier sections and the excess detail throughout. This, combined with the strongly North American orientation of the book, particularly in terms of epidemiology and medication, means it will be of little value to the European primary care physician.

C E CLARKE

Localization of brain lesions and developmental functions. Edited by D RIVA and A BENTON. (Pp 165, £39.00.) Published by John Libbey, Eastleigh, 2000. IBSN 0 86196 5999X

The richness of this subject has become apparent with the development of tests assessing an increasing array of aspects of cognitive function. This, coupled with intelligent use of structural and to an increasing extent functional, brain imaging, encourages the development of developmental brain/behaviour modules as never before.

It is timely then to have a book which reviews progress in the area—even if only to show the gaps in our understanding and the vast amount of work remaining to be done.

Arthur Benton, the doyen of localisation, provides an interesting historical perspective in an introductory chapter.

There follows one of four chapters by his coeditor Daria Riva, the first on memory and temporomesial structures. The clinical literature is usefully presented; general conclusions are offered as fact rather than as the hypotheses they are—although none the less interesting for that—namely, that the cerebral cortex stores information which is then codified in parahippocampal structures. The function of the hippocampus is to analyse the components of experience and to construct relations between different aspects of experience in flexible and potentially infinite ways, thereby creating a uniquely personal mental map.

Then follow three essays on lateralisation of hemisphere function as derived from studies of callosal deficits—congenital and acquired. The picture which tends to emerge from congenital agenesis of the corpus callosum is one of duplication of function in the separate hemispheres, with a general impoverishment of function. The extent to which this (or lateralisation) occurs may depend on maximal use of subcortical commissures and ipsilateral projections. That tests requiring interhemispheric transmission of visuomotor information take longer in children with agenesis, but shorter than in callosotomy patients may be explained by a better ability to use such compensatory pathways during development than in later life.

Three essays address the issue of language development, the hope being that children with early acquired brain lesions will shed light. Initial studies selected children with hemiplegia creating the myth that children had non-fluent aphasias only. Paquier and Van Dongen analysed the sparse literature on fluent aphasia in children and point out that this arises in conjunction with posterior lesions in 25 of 33 cases. Conversely, in the majority with non-fluent aphasias lesions are in prerolandic or perirolandic structures. A similar echo of adult organisation is found in the analysis of the 16 reported cases of subcortical aphasia by Martins. Lesions in anterior subcortical structures tend to produce non-fluent aphasias with preserved comprehension, whereas lesions in posterior structures lead to fluent aphasias with impaired comprehension perhaps by interrupting auditory pathways in the temporal isthmus. Unless both anterior and posterior structures are involved recovery is better than in adults. Also, unlike adults, major behavioural problems are rare.

The pattern begins to differ radically from adult aphasiology if the effect of lesions acquired prelingually—either prenatally or perinatally—are studied. The position, summarised by Reilly, is that both right and left hemisphere-damaged children initially show delay in comprehension and speech and show more grammatical errors of the kind shown by younger undamaged children. However by 7-10 years their language function is within the normal range. This suggests that brain areas required to develop language are more broadly distributed than those used to maintain language, that normality by 7-10 suggests a degree of plasticity, and that acquisition of language has fairly rigid processes with developmental deficits being those of timing rather than of kind.

Byron Rourke tries to summarise 29 years' work on right hemisphere non-verbal learning disabilities in seven pages. The picture which emerges is one of deficits in visiospatial function, tactile, perceptual and coordination difficulties particularly on the left, and furthermore a behavioural stereotype with difficulty in dealing with new solutions, difficulty in using feedback in complex situations, poor time concept, poor language pragmatics, phonetic misspellings, poor prosody and poor social skills, with conversely a good rote memory and a tendency to repetitive verbosity (this must bring to mind someone you know!). Lack of space in his account is compensated for by plenty of references.

There is a rehearsal of agnosias as defined by the adult neurology literature by Nichelli and Riva. They found no well documented accounts of agnosias in childhood and only two cases of non-lesional and presumed developmental prosop agnosia. An opportunity for someone.

Head injuries causing prefrontal damage are dealt with by Levin and Chapman. They document the damage to executive function and correlates with the degree of recovery from age 7-13. Dorsolateral prefrontal injury in infant monkeys only manifests in the adult. They are following up their children to see if a similar phenomenon occurs in humans.

Finally, arguments for the influence of the cerebellum on the cognitive development is summarised. Riva again contributes his clinical experience suggesting that after left cerebellar astrocytoma resection there is impairment of right hemisphere skills, whereas conversely after right cerebellar resection there is deterioration of left hemisphere skills.

It makes me uneasy that several of the authors present their own clinical experience, which in this format is non-peer reviewed. Indeed, published here it may not be presented elsewhere which also makes for access difficulties if your own library happens not to take this book. This rather begs the question of the function of collections such as these. Perhaps the Mariani Foundation should consider putting out future publications in their entirety on the Internet.

R O ROBINSON

Neurological emergencies, 3rd edition. Edited by RAC HUGHES. (Pp 399, £35.00.) Published by BMJ Books, London, 2000. ISBN 0 7279 1405 7

This is the third edition of a book which stems from an original series of 12 articles on *Neurological Emergencies*, published by this *Journal* in 1993. In this current edition there are 13 chapters; the "new addition" is the short final chapter by Dr O'Brien on criteria for diagnosing brain stem death. The titles of the other chapters have remained the same as they were in 1993 and cover a broad range of neurological, psychiatric, and neurosurgical emergencies. The authorship has changed remarkably little; but why change a winning team? The contributors are leading authorities in their respective topics.

Each chapter has been updated where necessary and all are well referenced. The summary boxes are particularly useful. This combination of strengths is appropriate, as the text is clearly not intended to be exhaustive. In the acute situation, the tables of differential diagnoses (the chapter on acute neuromuscular respiratory paralysis deserves special mention in this regard), boxes devoted to management (I continue to find the section on management of tonic-clonic status epilepticus very helpful), and the flow charts (notably the prediction of outcome of coma—invaluable for the intensive care consultation) are quickly located and will be extremely useful. The text adds "meat to these bones", but if more detailed information is required this could always be found from the references, hopefully after the crisis has passed.

From the title of the book, it will be purchased by predominantly neurologists. Thus, the chapters on traumatic brain injury and raised intracranial pressure may be less often read than the others. This is a pity, as these issues are well covered and have been extensively revised and updated.

There are always going to be minor quibbles with omissions and the relative weighting of topics from a multiauthor book such as this. I could not, for instance, find any reference to the diagnosis and management of neuroleptic malignant syndrome. It could be argued perhaps that more space could have been devoted to HIV infection and its management than the three pages allocated, compared with twice this space on brain abscess.

The book is compact and paperback, but will require a bag or briefcase for visits to the intensive care unit and accident and emergency department, as it is still too large to be accommodated by most white coat pockets. A strong case could also be made for keeping a copy on the neurology (and neurosurgery) ward rather than in the library. Specialist registrars may well wish to invest in their own copy. In the next few years, due to a combination of changing junior doctors' hours and the finite duration of training imposed by our current training system, it might also be wise for the consultant to keep a copy on their bedside cabinet!

DAVID J BURN

Dementia, 2nd edition. Edited by JOHN O'BRIAN, DAVID AMES, and ALISTAIR BURNS (Pp 940, £155.00). Published by Arnold Publishers, London, 2000. ISBN 0 340 759216X.

Dementia is a big subject and this is a big book. The first edition was edited by Raymond Levy and Alistair Burns and for this edition Professor Levy's retirement has catapulted John O'Brien and David Ames into sharing the editor's role. It is a role that seems to have been fulfilled excellently. Since the last edition the dementia field has not so much moved as leapt forward and this text valiantly does its best to keep up. To a certain extent this is an impossible task. It is simply not possible to keep abreast of the rapid developments in the fields of molecular genetics and biology. It could be argued that to do so is pointless as those who want and need to know of the latest developments will access journal or web based information. Instead, a text book, to my mind at least, should provide a repository for all those esoteric bits of knowledge, the general reviews allowing access to an area not one's own and the basic principles underlying a subject. This multiauthored text does all of those and it is those chapters that try to set out the general principles that succeed the best. Reading the chapters on topics as diverse as semantic dementia and spectroscopy was a much welcomed (and needed) educative exercise. There were many others. Not surprisingly however, the usual caveats to a text book review apply. It is expensive and, as in all multiauthored texts, some chapters are better than others. I particularly welcomed the learned chapter on the history of dementia by Berrios, the chapters on the different approaches to dementia from around the world make fascinating reading and the chapters on practical aspects such as design of environments for people with dementia and driving are excellent. One or two parts reflect more closely their author's strongly held viewpoints but diversity is always to be welcomed and this does not prevent me from concluding that this excellent book is truly an essential library purchase.

SIMON LOVESTONE

Clinical approach to antiphospholipid antibodies. Edited by STEPHEN R LEVINE and ROBIN L BREY (Pp 184, £55.00). Published by Butterworth Heinemann, Oxford, 2000. ISBN 0-7506-7177-7.

This monograph devoted to antiphospholipid antibodies (APA) developed from an annual course at the American Academy of Neurology and a collaborative study group, Antiphospholipid Antibody and Stroke Study (APASS). In these formats, the two editors addressed clinical questions about the specificity, utility, and clinical consequences of APA. The book is a compilation of multiauthor chapters that provide a useful compendium of information published about APA. Although the title of the monograph *Clinical approach to antiphospholipid antibodies*, suggests practical information, the central question, "What are the effects of these antibodies in patients?" remains largely unanswered. This, however, is not due to a lack of attention or diligence. The first two sections review the epidemiology and immunology, detailing the evolving story of the detection and the binding patterns of the antibodies. In particular the chapter on the immunology of the APA provides some useful basic facts (cardiolipin is restricted to mitochondrial membranes) and discussions about why individual APAs differ with respect to both immunological and anticoagulant properties. Antiphospholipid antibodies are actually an array of antibodies directed against negatively charged phospholipids (essential constituents of cell membranes) and usually requiring a cofactor such as prothrombin, β_2-glycoprotein 1, activated protein C, protein S, or annexin V to exert an immunological activity. Although the authors explain the basis for why these antibodies could either have a neutral, anticoagulant, or procoagulant effect, they also recognise that the antibodies could be a normal response to cryptogenic epitopes. The details of the role of (usually) cofactor β_2-glycoprotein 1 are presented clearly. The section on mechanisms of thrombosis and experimental models explains that APAs are heterogeneous and not all are associated with thrombosis or other clinical manifestations. The crux of the issue! In the array of clinical features associated with the coagulopathy, CNS and placental vasculopathy, and cardiac valvulopathy, a plethora of APAs have statistical associations but are they pathogenic? Is the effect elusive because the targets involve cascades of pathways and are thus subject to numerous biological variables? Possibly. Studies in animal models indicate that in specific circumstances the APAs can induce in vivo changes. However, in the chapter reviewing treatment, the marginal effects of immune therapies (including high dosage corticosteroid} and anticoagulant/antiplatelet therapies on preventing disease recurrence in patients induces reflection about the role of the antibodies we measure clinically. The authors detailing the clinical and pathological features of primary antiphospholipid antibody syndrome (APS), secondary APS, catastrophic APS, and regular thrombotic and embolic events associated with APAs recount the many anecdotes, small series, and clinical suspicions that represent the state of the art. Again, it is very useful to have these studies presented in one place so that both novice and experienced clinicians can appreciate current information and anticipate future studies. The book is short but not quickly read. My only reservation is that more information on the APASS study would have been useful in the monograph.

PATRICIA M MOORE

Stroke. Edited by MARTIN M BROWN (Pp 576, £34.95). Published by the Royal Society of Medicine Press, London, 2000. ISBN 1 85315 457.

The *British Medical Bulletin*, published quarterly, on behalf of the British Council, has a somewhat institutional ring to its title and a certain perversity in commencing, as this expert review does on page 275: "A bulletin (Italian; Bulletino) is a short official statement or periodical publication of a club." Professor Martin Brown, Scientific Editor, has "clubbed" together a wide choice of contributors from many disciplines though only one pathologist. The aim of this, the millennium publication, is to emphasis a British approach to cerebrovascular disorders through "the practical application of evidence based medicine combined with multidisciplinary management and rehabilitation".

Charles Wolfe kicks off with an excellent account on the socioeconomic impact of stroke; in particular drawing attention to both current primary and secondary care service provision. Thereafter there is an abstract somewhat impenetrable account on measuring outcome followed by an excellent highly recommended review by Alastair Lammie on the pathology of small vessel disease.

Next, the complexity of different animal models are succinctly discussed before embarking on the use of modern investigative techniques. These 60 or so pages are informative, up to date, and practically relevant with the exception of the section on MR spectroscopy, which seems too experimental in emphasis.

The next section of the book, of particular value to the stroke physician, deals with the current state of therapeutics. This covers thrombolysis, neuroprotection, antithrombotic drugs, and the neglected and well described area of optimising homeostasis. Peter Langhorne then addresses authoritatively the organisation of acute stroke care, this being of particular value to any clinician in dialogue with purchasers over establishing services. Dr Langhorne addresses home versus hospital care, the effectiveness of stroke units, and how to develop a service with respect to practice, procedures, and discharge planning. The following chapters deal with the surgical management of intracerebral haemorrhage (promoting the ongoing multicentre prospective randomised control trial evaluating whether or not early clot evacuation improves outcome), swallowing, nutrition, management of spasticity, prediction of outcome and stroke prevention with respect to antiplatelet agents, carotid endarterectomy, angioplasty, and stenting (reflecting the editors' particular area of interest) and anticoagulation. These are excellently referenced and at each conclusion, draw attention to "key points for clinical practice". The final chapter by Shah Ebrahim reviews the cost effectiveness of stroke preventions, initially introducing the non-economist to the need for and principles of economic appraisal. I found this particularly informative and table 6, summarising the cost effectiveness of a range of preventative interventions of great value.

All in all, this is an excellent publication doing justice to the importance of the millennium volume of the bulletin. It pulls together strands of current knowledge allowing informed evidence based practice The chapter format, adhered to throughout, is clear, easy to follow, and key points for clinical practice thoughtful. Professor Brown and his colleagues have achieved their objective in producing a readable, accessible series of expert reviews. Criticisms, yes; if the emphasis here is to outline the "British approach", more attention should be directed to current haphazard practice with respect to the availability of acute stroke units, the paucity of neurologists actually involved in stroke care when compared with European and North American counterparts and the lack of proper structures and systems to triage complex, often young, patients with stroke acutely to Regional Neuroscience Centres. Also, there is nothing here that addresses the type of stroke neurologists in the United Kingdom are most often asked to review—namely, those with atypical cerebrovascular disorders. I would like to have seen more in relation to

young patients with stroke, inherited cerebrovascular disorders, and vascular dementia. However, as the text stands, it is highly recommended to those who practice cerebrovascular medicine.

IAN BONE

An atlas of Alzheimer's disease. The encyclopedia of visual medicine series. Edited by MONY J DE LEON (Pp149, £59.00). Published by Parthenon Publishing, Carnforth, 1999. ISBN 1-85070-912-2.

In just 149 pages and nine separately authored chapters, Professor De Leon has produced a practical guide to the clinical, radiological, and pathological features of Alzheimer's disease, principally aimed at junior hospital doctors, nurses, and other paramedical workers, as well as general practitioners, with an interest in the disorder. The book is beautifully illustrated, and the many diagrams are helpful and informative. Reisberg relates the changes in daily life that affect patients with Alzheimer's disease, from the very beginnings of change through to the very end of life. The accompanying drawings are delightful and bring home the misery of the illness in a very real way. The utility of functional imaging in persons at risk of Alzheimer's disease is discussed and lavishly illustrated by Jagust. A detailed anatomy of the hippocampus and associated structures by De Leon follows, chronicling the early involvement of these regions and emphasising the value of MRI in differentiating persons with mild cognitive impairment, as well as frank dementia, from cognitively intact people. However, here, the reader is left with the (misleading) impression that MRI can act as a sensitive diagnostic for Alzheimer's disease, neglecting that equivalent degrees of hippocampal atrophy can occur in patients with other forms of dementia—for example, frontotemporal dementia. Braak eloquently covers the topographic origins and spread of the pathological changes. Iqbal reviews the structure of the neurofibrillary tangle and its affects on neuron function. The role of glial cells in the formation and removal of amyloid is discussed by Wegiel and its chemical properties by Wisniewski. Poirier reviews genetic factors, although the book suffers somewhat here from the advances made in this area since its publication in 1999. For example, the number of causative mutations in the presenilin-1 gene listed has now nearly trebled and the identity of the presenilin proteins, their function, and relation to amyloid formation are much better understood. None the less, overall, this is an excellent book that will have great appeal. I would recommend a look, even its purchase, particularly as the author's royalties are being donated towards the establishment of a young researcher fund.

DAVID M A MANN

Neural transplantation methods. Edited by: DUNNETT, BOULTON, and BAKER (Pp 556, US$125.00). Published by The Humana Press, New Jersey, 1999. ISBN 0 896 03793 2.

Just over 20 years ago, the notion that nerve cells transplanted to a damaged adult brain could not only survive but also make functional connections would generally have been regarded as heretical. Since that time, however, the field of embryonic neural transplantation has grown almost exponentially and has emerged as a credible discipline. Aside from considerations of functional repair to brain damaged hosts, the technique has also been revolutionary as a tool for investigating neural development and specific aspects of neurodegeneration.

This *Neuromethods* volume is the 36th in an ongoing series and has an internationally acclaimed neuroscientist as first editor. In particular, Professor Stephen Dunnett was instrumental in establishing embryonic neural transplantation as an experimental technique from its earliest days in the late 1970s and has remained its leading scientific figure in the United Kingdom. The volume itself is clearly devised as a handbook for aspiring neural transplant surgeons or those wishing to hone their techniques. Rather than serving merely as a manual, however, it also provides a timely historical review and exhaustive reference source for this young science. It is divided into three sections which, respectively, focus on the numerous possibilities for obtaining neural cells for transplantation, the techniques of implanting the neural tissue, and, lastly, tips for enhancing neuronal survival and connectivity.

The first of these aspects is perhaps the most controversial, especially with respect to potential clinical applications for neural transplantation in Parkinson's and Huntington's diseases. It has been abundantly clear from the earliest use of this technique in human patients that obtaining embryonic tissue would provide extreme practical problems and cause the most ethical concern. It is extremely useful, therefore, to find up to date chapters on neural stem cells, immortalised cell lines, and engineered cells as sources for transplant material. Similarly, the chapter on intracerebral gene transfer using various viral vectors provides an alternative approach to studying development and even repair, representing a potentially exciting tool for the future.

The section on transplant methods serves as a useful review of a technique for introducing transplant material to the host. It also includes a chapter on glial transplants as an experimental method for the remyelination of central nervous tissue. In general, this section draws on the considerable experience from the leading laboratories in the field and underlines the expertise required to undertake successful grafting using techniques which, to the uninitiated, may seem deceptively simple. In addition, one chapter revisits the early technique of intraocular grafting which, as an in vivo model, has several advantages. In particular, the accessibility and ease of visualising graft growth in this model allows many of the basic scientific questions on neural transplantation to be addressed.

The final section on the factors governing graft survival and function is, by necessity, perhaps the most speculative. The reason why over 90% of grafted embryonic neurons fail to survive remains largely obscure and is almost certainly multifactorial, reflecting host and graft factors. The potential role of apoptosis is discussed in some detail as are the various methods of inhibiting this process by specific means such as captase inhibition or the use of trophic factors. The chapter by Brundin explores the nature and timing of transplant cell death and includes discussion of antioxidant strategies. The potential utility of combining several neuroprotective approaches is pertinently addressed. Several other chapters in this section centre on the difficult issue of immunological rejection of transplant tissue by the host. The likely need for genetically engineered transplant tissue for successful grafting across species is discussed despite the relatively low immunogenicity of embryonic neural tissue and the (semi) privileged transplant sites within the blood-brain barrier. These issues are particularly pertinent to the potential clinical use of embryonic porcine neural tissue in human neurodegenerative disease.

In conclusion, this book provides an exhaustive summary of the neurobiological theory and techniques, both established and potential, relating to neural transplantation. It is clearly a highly specialised area now emerging from its infancy and is unlikely to have general appeal to clinical neurologists. However, certainly for those intending to use this immensely powerful technique in the context of basic neuroscientific research, the book will be invaluable. Similarly, for those with an interest in the potential application of neural (or glial) grafting in human disease, the volume will provide an excellent rationale for the technique and give a state of the art account of where we stand. The illustrations are generally of extremely high quality and the references extend to 1999. If the volume is read sequentially there is a degree of repetition among the numerous authors but this would be my only quibble. If the field of neural transplantation "takes off" in the decades to come, as many think, this volume is likely to find itself a classic, heralding the definitive arrival of this novel and innovative technique.

PAUL READING

Alzheimer's disease and related disorders annual. Edited by SERGE GAUTHIER and JEFFREY L CUMMINGS (Pp 255, £39.95). Published by Martin Dunitz, London, 2000. ISBN 1-85317-909-4.

My first impression on being asked to review this book was "who needs another text book on dementia?" this opinion quickly changed as I browsed through the 11 chapters and often alighted on actions that caught my attention. After several browsings I found that I had actually read substantial chunks of virtually every chapter.

The greatest virtues of the book are the choice of topics, which encompass almost all of the rapidly evolving and controversial areas in dementia research including the genetics of Alzheimer's disease; chromosome 17 and frontotemporal dementia; dementia with Lewy bodies; mild cognitive impairment; the status of subcortical vascular dementia; neuropsychiatric manifestations of Alzheimer's disease; and therapy with cholinesterase inhibitors, hormones, and anti-inflammatory drugs. Secondly, the fact that all of the chapters are written by acknowledged experts in the field. Thirdly that the coverage is international (with contributions from the United States of America, Canada, the United Kingdom, Germany, France, Finland, and Italy); and most notably, the short delay between writing and publication is evidenced by the inclusion of many references from 1998 and some from 1999.

The book provides, therefore, excellent summaries of recent advances in each of the topics covered, all of which are covered in an accessible style. For those involved in research in one particular area (which is these days inevitably limited in scope) it is valuable to have such a collection of fully referenced reviews from the broad range of other topics. It is clearly not aimed at trainees, who are likely

to be rather confused by the contradictory ond rapidly evolving state of affairs in areas such as mild cognitive impairment and subcortical vascular dementia. I can recommend it warmly to established clinicians and researchers with an interest in dementing diseases.

JOHN HODGES

Clinician's manual on anxiety disorders and comorbid depression. Edited by DAVID NUTT, SPILIOS ARGYROPOULOS, and SEAN HOOD (Pp 56, £ 7.25). Published by Science Press, London, 2000. ISBN 1 85873 397 9.

This is a small book with a formidable task. The editors describe it as written for "busy clinicians, especially general practitioners". The layout of the book is certainly clear and the writing mostly jargon-free as intended. Chapters are arranged roughly in accordance with the divisions of chapter F40-48 of ICD-10: "Neurotic, stress-related and somatoform disorders". These initial chapters cover the symptoms, diagnosis, epidemiology, comorbidity, and aetiology of each of the five main disorders covered. A useful if perhaps somewhat confusing chapter deals with the important subject of comorbid depression and anxiety. The final chapter, which will almost certainly be the most heavily thumbed, deals with treatment. The book includes many clear diagrams and tables and the final treatment chapter includes some easy to follow treatment algorithms.

There is no doubting the psychopharmacological emphasis and expertise of this book, as would be expected from the editors. Psychological aetiologies and treatments appear as appetisers to virtuoso descriptions of the latest theories and applications of drug treatments. In the section on psychological treatments it is stated that "unfortunately, many of the psychological techniques used require specialised training, and access to practitioners with these skills is often difficult". This is arguably the case, but in practice psychological interventions probably still come somewhat higher up the treatment algorithm than 6 to 12 months of high potency benzodiazepines. The rationale for judicious use of benzodiazepines as the most potent anxiolytic agents is argued and the words tolerance and dependence do not appear in this context.

In summary, this is a satisfyingly concise text with a good balance of scientific facts and interesting historical detail. The busy clinician will find it an invaluable guide to pharmacological treatments of anxiety disorders but will they really wait so long before referring to a clinical psychologist for adjunctive treatment?

ELIZABETH VENABLES
CHRISTOPHER BENCH

Pediatric epilepsy: diagnosis and therapy, 2nd edition. Edited by JOHN M PELLOCK, W EDWIN DODSON, and BLAISE F D BOURGEOIS (Pp 688, US$150.00). Published by Demos Medical Publishing, New York, 2001. ISBN 1-888799-30-7.

The most useful part of this book is an account of each of the anticonvulsant drugs. Concisely summarised is the evidence for efficacy, or lack of it, of each. Included is a section on epilepsy surgery.

It is approached by a section on general principles, which is a miscellany including (oddly) status epilepticus but also treatment decisions, anticonvulsant profiles, dosage considerations, pharmacokinetics and some treatment decisions. These two sections comprise the "therapy" of the title.

Preceding that is a section on epilepsy syndromes, including a discussion on epilepsy classification and epidemiology and the place for EEG and neuroimaging—the "diagnosis" part of the title. Introducing these sections are chapters on cellular mechanisms, consequences of seizures, and genetic influences.

The preface suggests that the book is intended as a practical guide and reference for clinicians and investigators. The contributors are generally the names to be expected in the different fields, drawn largely from north America (none from Europe). Does it succeed? Not as well as it might.

As a practical guide it does not deal with the investigation of many epilepsy situations, such as the encephalopathic epilepsies of infancy—nor with rational drug strategies in partial and generalised epilepsies.

It is curiously lacking in many management issues such as "pseudo" seizures, "subclinical" seizures or transient cognitive impairment, or the implications of the abnormal EEG in autism—a particularly hot topic at the moment. It is silent on the question of life expectancy and the phenomenon of sudden unexpected death—issues which the clinician will be asked about. The management of status epilepticus is well described, but there is nothing about outcome—again a question uppermost in parents' minds. The section on quality of life is theoretical and research oriented. How to approach constraints in lifestyle and what may be done to ameliorate them is void.

The section on adolescents' needs, transitional clinics, and organisation of epilepsy clinics in general would have been welcome.

Vagal nerve stimulation, mentioned as a major new development in the preface, gets about two and a half column inches in the section on Lennox-Gastaut syndrome.

The book shows signs of lack of editorial grip. Sections on Landau-Kleffner syndrome or pyknolepsy are found in several places, all saying more or less the same thing. Although I suspect a subsidiary aim was to link basic and clinical sciences, there is no cross referencing between the two (or between any other chapters for that matter).

A major text in this subject deserves to do well, but I am afraid that in this instance the discriminating buyer will look elsewhere.

RICHARD O ROBINSON

Diagnosis and management of pituitary tumors. Edited by KAMAL THAPAR, KALMAN KOVACS, BERND W SCHEITHAUER, and RICARDO V LLOYD. (pp 479, US$225.00). Published by The Humana Press, Totowa, 2001. ISBN 0-896-03403-8.

This new multiauthor text attempts the ambitious task of reviewing in inclusive detail the wide range of pituitary function, dysfunction, clinical assessment, and management of pituitary tumours. The editors, three of whom are pathologists, are eminent in this field and they have assembled an outstanding list of contributors. A sound scientific background is provided in specific chapters, which are devoted to anatomy, physiology, pathophysiology, pathology, and molecular pathogenesis, and remains evident in the subsequent chapters dealing with medical, surgical, and radiotherapeutic approaches to management of specific tumour types. All chapters provide authoritative and valuable reviews and conclusions drawn are based on a thorough assessment of the literature. There are, of course, some overlaps between individual chapters with a common theme—for example, molecular pathogenesis—but this is not disadvantageous and allows each contribution to stand alone. This notwithstanding, the editors have achieved overall cohesion of presentation so that the book can be viewed as a whole and not simply a collection of reviews. It is inevitable that the time required to complete such a large project means that some important recent developments, such as the discovery of the natural ligand for the growth hormone releasing peptide receptor, could not have been included in the excellent chapter on hypothalamic-pituitary physiology and regulation. Any criticism of this book would be minor but I was disappointed that an otherwise very thorough chapter on neuro-ophthalmological evaluation did not deal with the more practical aspects of clinical assessment including choice of methods for field assessment. Overall, the editors have achieved their stated aim of providing information in a single book which is of value to the various specialists who treat patients with pituitary mass lesions and function as members of a multidisciplinary team. I would strongly recommend it to clinical endocrinologists, to neurosurgeons seeking an in depth knowledge of the endocrinological aspects of pituitary mass lesions, and to neuroendocrine pathologists who will appreciate the breadth of coverage and the extent to which discussion of pathogenesis, pathology, and clinical management have been skilfully combined.

JOHN MONSON

Handbook of ataxia disorders. Edited by THOMAS KLOCKGETHER (pp 689, US$215). Published by Marcel Dekker Inc, New York, 2000. ISBN 0-8247-0381-2.

There is a constant debate as to the value of textbooks in general in this information technology age. This is perhaps most marked in the field of molecular genetics, which is moving at such a pace that a chapter could almost be redrafted or updated on a weekly or at least monthly basis given the rapidity of new developments. Nevertheless there is value in collating all the current information and attempting to put a field in context. I think that such is the intention of a volume such as this. Klockgether has amassed an impressive field of contributors to this large volume on ataxic disorders. The book spans some basic neuroanatomy and neurophysiology of the cerebellum through clinical approaches to ataxic patients and then several chapters describing the many disorders that can affect the cerebellum and its connections, thus producing ataxia. Perhaps unsurprisingly given the area of progress in this field most of the chapters are given over to the genetic forms of ataxia and a relatively few to the non-hereditary ataxias. This of course does not represent the true pattern seen in a general or even specialist neurology clinic. However, I see no way around this as our knowledge of the non-hereditary is rather scant at present. This of course is in marked contrast with the progress over the past 5-10 years and our understanding of the genetic ataxias where we have seen identification of numerous forms of dominant and recessive ataxias. In most of the major areas the genes are identified and we have now moved into the field of

molecular biology to try and illuminate the pathogenic pathway. These experiments are brought up in the relevant chapters.

A constant problem in a multiauthor book such as this is a non-uniformity of style or perhaps even worse, repetition from one chapter to the next. I am pleased to note that this has largely been avoided and apart from a rather brief general introduction to most of the chapters which could apply to some others each author does not labour the point on the dominant ataxias, for example. However, sufficient information is given in each chapter to allow the reader to delve into that chapter alone to understand SCA 1 or SCA 3 for example. I think this is testimony to both good authorship and good direction from the editor. However, there are one or two minor irritations. For example, the referencing system in chapter 1 is different from other chapters. Also, within this chapter there is a small error but it makes part of the chapter difficult to read. The abbreviation for long term depression and long term potentiation are given as the same and therefore that section is more difficult to understand than it might be. These are small quibbles. My only other disagreement with the book came in chapter 27 when the author describes most late onset cerebellar degeneration as being cases of MSA. I would agree that a significant minority fall under this category but I think that there are larger numbers of patients in whom no definitive diagnosis can be made and yet do not go on to produce the other features of MSA. Overall I enjoyed this book and I think that it has a place in the library of a neurologist. It will probably be most attractive to those neurologists who see a significant number of ataxias or those who wish to update themselves in the general sense. However, it is quite expensive and I think that this may limit its attractiveness to the generalist.

NICHOLAS WOOD

The brain and cardiac surgery. Causes of neurological complications and their prevention. Edited by STANTON P NEWMAN and MICHAEL JG HARRISON. (pp 343, £70.00). Published by Harwood Academic Publishers, The Netherlands, 2000. ISBN 90 5702 476 4.

This book offers a description of the neurological syndromes that may occur after cardiac surgery, including both central and peripheral complications. This is followed by information on neuropsychological outcome, quality of life, imaging, and neuropathology. The information supplied is reasonably comprehensive. The data on prognosis are a little thin, but there is probably enough here to advise patients, and the relatives of patients who have sustained damage, for the information to be useful, although it would be available from other sources. The one complication that I did not see mentioned was hypertensive encephalopathy, which I have seen in a teenage patient with apparently "normal" blood pressure after cardiac transplantation, but who for many years preoperatively had a systolic blood pressure of about 70.

The next section of the book deals with markers of cerebral injury and patient monitoring techniques including both EEG and cardiac emboli; it subsequently moves on to management techniques. These two parts of the book would be of very limited interest to neurologists, and would be of greatest interest to anaesthetists. The information is fairly comprehensive although it deals with prevention, part of the subtitle of the book, implicitly rather than explicitly and similarly identification of high risk patients is covered very sparsely indeed.

Neurologists will be familiar from other environments with the vast majority of the neurological material in this volume. It will probably be of greatest use to anaesthetists and cardiac surgeons, for whom it would be a useful introduction to the neurological consequences of cardiac surgery.

JOHN BOWLER

Neurosurgical classics II. Edited by ROBERT H WILKINS and GLORIA K WILKINS. (pp 592, US$95.00). Published by American Association of Neurological Surgeons, Rolling Meadows, 2000. ISBN 1 897284 74 X.

The first volume of this book, which was published in 1965 under the auspices of the Harvey Cushing Society, now The American Association of Neurological Surgeons, republished 52 papers of outstanding interest in the history of neurosurgery which had been published before 1940. Those papers which had been originally printed in languages other than English were translated into the English language. Because of demand the first volume was reprinted in 1992.

This second volume of *neurosurgical classics* reprints a further 58 papers published since 1940. These papers are divided into 31 groups each of which is preceded by an introduction outling relevant background material and references. Rather curiously, the references for the papers are given in the contents section but are not attached to each individual paper.

A wide range of topics is covered. Thus, in the first section on diagnostic techniques we have the first papers on CT published by Hounsfield and Ambrose in 1973 and the subsequent pioneering papers on MRI published over the next few years. Other topics covered include papers on intracranial pressure, topical haemostatic agents, microneurosurgery, skull base surgery, and the first descriptions of anterior operations for cervical disc disease. The original illustrations are used although in some cases eye covers have been added to the photographs to protect the identity of the patients. This is perhaps a little superfluous as most of the patients concerned have probably been dead for many years as a result of the time that has elapsed since publication and the conditions for which surgery had been carried out. Some of the papers have been shortened and a handful of papers are included from the pre-1940 era going back as far as 1910—for example, Halstead's report of two cases of pituitary tumour operated on by the transphenoidal route.

This book makes fascinating reading. It is hard to believe that there is a neurosurgeon who will not want to possess a copy or having obtained it, will not want to reread some of the articles. It is perhaps a pity that the first volume was not republished as a companion to the present one so that it would have been possible for those of us who do not possess the first volume to purchase both at once. Many, perhaps most, of the papers it contains are of such abiding interest that they are still often quoted in lists of references. To add to its desirability it is beautifully produced and printed and sufficiently well bound to make it a robust bedside book.

R S MAURICE-WILLIAMS